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RETROSPECTIVE STUDY

The frequency of, and predisposing risk factors for, ciprofloxacin-induced neuro-psychiatric adverse drug reactions

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ABSTRACT

OBJECTIVES: Ciprofloxacin induces rare neuro-psychiatric adverse drug reactions (ADRs) that are, as yet, not possible to predict due to unknown predisposition factors.

BACKGROUND: The aim of the analysis was to assess the frequency of neuro-psychiatric ADRs and to identify potential risk factors that predisposed patients to ciprofloxacin neurotoxicity.

METHODS: This observational retrospective study involved the evaluation of the medical records of patients in the Nephrology department and 3rd Internal Clinic of the General University Hospital in Prague.

RESULTS: The overall incidence of neurological ADRs was 3.6 %. No neurological ADRs developed in patients aged less than 70 years. The covariates that were significantly more prevalent in the patients who developed neuropsychiatric ADRs were as follows: higher age, a history of neuropsychiatric disorders and the use of anticonvulsants. The administration of drugs from other ATC groups, gender, weight, body mass index, body surface area, renal functions, level of C-reactive protein at the beginning of treatment and the total daily dose/kg did not differ significantly between the two groups.

CONCLUSION: Ciprofloxacin neuropsychiatric ADRs are more frequent in older patients with a history of neurologic or psychiatric disorders. No other tested covariates were proven to predispose patients to neuropsychiatric ADRs during treatment with ciprofloxacin *(Tab. 2, Ref. 20)*. Text in PDF *www.elis.sk*

KEY WORDS: fluoroquinolones, delirium, neurotoxicity, kidney disease, infection.

Introduction

Ciprofloxacin is a fluoroquinolone antibiotic that continues to be an important agent in the treatment of serious and life-threatening infections. Nevertheless, the European Medicines Agency recently released a set of warnings concerning potentially serious ciprofloxacin-related adverse drug reactions (ADRs) and recommended that its use be restricted. Ciprofloxacin, as well as other fluoroquinolones should no longer be used to treat mild or moderate bacterial infections if safer alternatives can be used instead (1). In addition to ADRs affecting the joints, tendons and QT prolongation, ciprofloxacin causes a wide spectrum of neuro-psychiatric ADRs, i.e. confusion, headache, organic psychosis, manic episodes, drowsiness, vertigo, depression and even seizures (2–10). Neuro-psychiatric ADRs may be linked to larger doses (7, 8), kidney or liver dysfunction (3, 6–8) and a history of disease that affects the central nervous system (CNS) (7, 9).

The degree of penetration of ciprofloxacin into the CNS is poor and its concentration in the cerebospinal fluid reaches only 10% of the plasmatic levels thereof (11). It is metabolized to four main metabolites (12) largely by CYP 1A2 (13). A more detailed description of the ciprofloxacin metabolism is lacking. Its non-renal clearance provided for around 40 % of the total body clearance following intravenous administration to healthy volunteers (14–16). Therefore, the ciprofloxacin PK is significantly influenced by renal insufficiency (17). It attains higher concentrations in the plasma and cerebrospinal fluid of rats with liver and renal failure; however, the ratio of unbound ciprofloxacin in the CNS and plasma is reduced in comparison to animals without

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compromised elimination organs. This may be due to decreased blood-brain barrier permeability (18). It is not clear if this is also the case in patients with chronic eliminating organ dysfunction, which may differ greatly from the acute states that are induced in laboratory animals.

The potential mechanisms of fluoroquinolone neurotoxicity comprise GABA signaling inhibition and MNDA signaling activation (19), which may explain the decrease in the seizure threshold and development of seizures in predisposed patients (9, 20). It is unlikely that other types of neurotoxicity, e.g. psychosis, can be explained by these mechanisms since NMDA activation should act to calm down rather than activate psychotic symptoms (20).

The aim of our retrospective analysis was to evaluate the occurrence of neuro-psychiatric ADRs in patients treated in the hospital's nephrology and internal medicine departments and to identify the potential risk factors that predispose patients to ciprofloxacin neurotoxicity, especially kidney dysfunction, the severity of infection and a history of neuro-psychiatric disorders.

Materials and methods

This was an observational retrospective study evaluating the medical records of three cohorts of patients at the General University Hospital in Prague: Cohort 1 (the control group) comprised all patients in the Nephrology department that were administered ciprofloxacin between 2017 and 2018; patients who *did not* develop neuropsychiatric ADRs were included. Cohort 2 was made up of all those patients that were administered ciprofloxacin in the Nephrology department between 2017 and 2018 and who *did* develop neuropsychiatric ADRs. Cohort 3 comprised all the patients hospitalized in the Nephrology department and 3rd Internal Clinic between 2019–2021 who had history of, or had recently developed, neuro-psychiatric ADRs potentially related to ciprofloxacin treatment. Cohort 2 was compared with cohort 1 so as to determine the incidence of neuropsychiatric ADRs. Patients from cohorts 2 and 3 were then compared with those in cohort 1 in order to identify the predisposing risk factor. Upon admission to the hospital, the patients signed informed consent forms wherein they agreed, *inter alia*, that their anonymous data could be used for research purposes including the publication of the research results.

The covariates tested comprised: gender, a history of neurologic disorders (seizures, spasticity, Parkinsonism etc.), a history of psychiatric disorders (dementia, affective and psychotic disorders, GAD, OCD), medication with benzodiazepines (BZDs) or Z-hypnotics, opioids, corticosteroids, antidepressants, antipsychotics, anticonvulsants (including clonazepam and anticonvulsants for non-epileptic indications) and age, weight, body mass index (BMI), body surface area (BSA, according to the Du Bois formula), estimated glomerular filtration rate (eGFR) according to the CKD-EPI formula, C-reactive protein (CRP) at the beginning of ciprofloxacin treatment and a daily dose with a correction factor of 0.7 for oral administration (to correct for the lower bioavailability (16)) and normalized for the body weight. The Student's t-test was used for the continuous covariates. The eGFR value was set at zero if the patients received renal replacement therapy. Concerning the other covariates, the chi-square test with the Yates correction and the two tailed P-value was used for the determination of the statistical significance, which was set at 0.05.

Tab. 1. Percentage of patients who developed neuropsychiatric ADRs related to ciprofloxacin treatment.

AGE	No of patients without neuropsychiatric ADRs (cohort 1)	No of patients with neuropsychiatric ADRs (cohort 2)	%
≥ 80	20	3	13.6
70–79	42	2	4.5
≤69	70	0	0
Total	132	5	3.6

Tab. 2. The covariates tested for ciprofloxacin-related neuropsychiatric ADRs with the level of statistical significance. The values are stated as the median (IQR).

Covariate	No of patients without signs of neurotoxicity (cohort 1)	No of patients with signs of neurotoxicity (cohorts 2 + 3)	p
No. of females/males	55/77	5/7	1.0000
history of neurologic disorders (seizures, spasticity, Parkinsonism etc.)	14/118	5/7	0.0094
history of psychiatric disorders (dementia, affective and psychotic disorders, GAD, OCD)	20/112	8/4	0.0001
BZDs or Z-hypnotics	17/115	4/8	0.1349
opioids	14/118	4/8	0.0682
corticosteroids	42/90	5/7	0.7076
antidepressants	21/111	1/11	0.7800
antipsychotics	16/116	4/8	0.1100
anticonvulsants (including clonazepam and anticonvulsants for non-epileptic indications)	1/131	2/10	0.0083
age	68 (54.75-75)	75 (67.25-83.5)	0.0385
weight	79 (66-95)	76 (68.5-89.5)	0.8392
BMI	23.1 (27.5-31.1)	27.4 (24.3-32.2)	0.8618
BSA	1.9 (1.8-2.1)	1.9 (1.7-2.0)	0.7372
eGFR	23 (0-51)	39.5 (8.8-60.0)	0.4942
CRP	91.7 (28.6-151.6)	164.0 (57.6-204.8)	0.2170
total daily dose/body weight*	11.1 (9.7-13.6)	13.2 (10.4-14.4)	0.4336
PO/IV/NA administration	66/61/5	5/7/0	0.7037

* the dose was corrected with a factor of 0.7 if administered perorally. PO – peroral; IV – intravenous; NA – not available; BMI – body mass index; BSA – body surface area according to the Du Bois formula; eGFR – estimated glomerular filtration rate (according to the CKD-EPI formula), CRP – C-reactive protein; BZD – benzodiazepine; GAD – generalized anxiety disorder; OCD – obsessive-compulsive disorder

Results

A total of 139 patient records were screened between 2017 and 2018 by the Nephrology Department. Two patients were excluded from the analysis due to delirium that was caused by an apparently different reason than ciprofloxacin toxicity (one had a subdural hematoma and the other was confused prior to the initiation of ciprofloxacin therapy due to severe sepsis; the patient subsequently had to be sedated due to the progression of the severity of the disease). 132 patients were included in cohort 1 and 5 in cohort 2. The percentages of patients with neurotoxic ADRs calculated from number of patients in cohorts 1 and 2 according to age group are listed in Table 1. The frequency of neuropsychiatric ADRs for the whole group was 3.6 %, which increased with advanced age. Neuropsychiatric ADRs were detected in this cohort only for patients over 70 years of age; an incidence rate of 4.5 % was determined for patients 70–79 years of age and 13.6 % for patients over 80 years of age.

A total of 7 patients were included in cohort 3. The covariates tested, with the levels of statistical significance, are listed in Table 2. The patients who experienced neuropsychiatric ADRs were from the older age cohort; a median (IQR) of 68 years (54.75–75) was determined for patients without ADRs and 76 years (67.25–83.5) for patients with ADRs ($p = 0.0385$). Concerning patient history, neurologic and psychiatric disorders were found to be closely associated with a higher probability of ciprofloxacin-induced neuropsychiatric ADRs and, with respect to concomitant pharmacotherapy, only anticonvulsants were seen to be associated with neuropsychiatric ADRs caused by ciprofloxacin. Nevertheless, only a very low number of patients in the two groups used anticonvulsants. Therefore, the association with anticonvulsants may have been merely a random finding.

We observed two distinct types of neuropsychiatric ADRs. All the symptoms in the patients over 70 years of age had the nature of psychiatric disorders (either delirium or psychosis) while the younger patients included in the analysis suffered more frequently from significant worsening of a pre-existing neurologic disorder (e.g. Parkinsonism or spasticity).

Discussion

This study provides a description of the frequency of the occurrence of ciprofloxacin neuropsychiatric ADRs in the surveyed nephrology department over a period of 2 years. The total incidence of ciprofloxacin neurotoxicity was 3.6 %, which is higher than stated in the SmPC of ciprofloxacin, i.e. the frequency of both neurologic and psychiatric disorders is stated at less than 1 %. The manifestations varied widely from purely psychiatric disorders, including psychosis with hallucinations and hetero-aggressive delirium, to purely neurologic symptoms, particularly the worsening of pre-existing neurologic disorders (Parkinsonism, spasticity).

Concerning patient characteristics, we identified a significant relationship between ciprofloxacin-induced neuropsychiatric toxicity and advanced age, a history of psychiatric and/or neurologic disorders and co-medication with anticonvulsants; the latter was determined only by chance considering its very low incidence in both groups of patients. Since advanced age is commonly connected with neuropsychiatric illnesses (7, 9), it is likely that these variables are not fully independent.

The association of ciprofloxacin with neuropsychiatric ADRs was suggested in case reports or case series (3, 6, 7). Surprisingly, in contrast with these findings, we did not identify a relationship between the development of neuropsychiatric ADRs and the severity of kidney dysfunction even though the patients surveyed evinced a wide spectrum of eGFR values from end-stage kidney disease to normal renal functions; it is important to bear in mind in this respect that kidney dysfunction significantly impairs the elimination of ciprofloxacin (17). This is in line with the fact that we also failed to identify the association of neurotoxicity with higher doses. This clearly suggests that neuropsychiatric ADRs to ciprofloxacin are of an idiosyncratic nature, do not depend on the dose and plasma level and most frequently develop in elderly patients with pre-existing CNS-affecting disorders.

We recommend that further studies, including genomic and proteomic analyses, be conducted so as to elucidate the exact mechanism of fluoroquinolone-induced neurotoxicity and to identify potential markers that allow for excluding patients prone to neurologic toxicity from fluoroquinolone treatment. Before such markers are discovered, physicians should at least be aware of the high risk of psychiatric symptoms in elderly patients and patients with a history of neurologic or psychiatric disorders treated with ciprofloxacin.

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