Adverse reactions of fluoroquinolones to central nervous system and rational drug use in nursing care

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Abstract: Fluoroquinolones are a kind of synthetic drugs commonly used in clinical treatment. They have good broad-spectrum antimicrobial properties. They are not only convenient to administer, but also have remarkable therapeutic effects. In this paper, we selected 70 patients with adverse reactions of central nervous system during the use of fluoroquinolones as the research object. We reviewed and analyzed the basic data, main manifestations and outcomes of adverse reactions, and summarized the influencing factors. The results showed that dizziness, irritability and insomnia were the main symptoms in 42 patients with mild adverse reactions. In 28 patients with moderate to severe adverse reactions, neuropsychiatric symptoms such as restlessness, depression, nervous excitation, phonism and hallucination were found. 54 patients were able to recover after stopping the medication. The remaining 16 patients were treated with drugs, and the effective rate was 87.5%. By analyzing the related factors, it can be seen that elderly patients over 60 years old, intravenous administration, combination of drugs and past history of neurological diseases are the main factors leading to adverse reactions of the central nervous system. In this survey, there were 7 kinds of adverse drug reactions, of which 31 cases (44.28%) were caused by levofloxacin. Therefore, fluoroquinolones have adverse effects on the central nervous system in the course of treatment, and the occurrence of adverse reactions is related to patients' age, route of administration, drug combination and past history of illness. It is important to grasp the above factors and make rational use of drugs.

Keywords: Fluoroquinolones, central nervous system, adverse reactions, influencing factors.

INTRODUCTION

Fluoroquinolones has many advantages, such as broad antimicrobial spectrum, strong action, low adverse reaction (ADR). With the widespread use of fluoroquinolones antibiotics (FQS) in clinical practice; more and more reports about its ADR have been reported (Barr *et al.,* 2015). In addition to the common gastrointestinal ADRs such as nausea, vomiting and anorexia, FQS can also trigger mental reactions, hallucinations, depression and convulsions (González *et al.,* 2017). In recent years, the incidence of neuropsychiatric ADR has been increasing. The incidence of neuropsychiatric reaction is generally 1%-2% (Jin, 2010; Klastersky *et al.,* 2016). The incidence of severe neuropsychiatric reaction is less than 0.5% (Goymann *et al.,* 2002). In clinical work, we tend to neglect its neuropsychiatric ADR and mistake it for various primary diseases or neuropsychiatric symptoms of unknown causes, leading to misdiagnosis. Fluoroquinolones antibiotics are one of the commonly used antibiotics in clinic. They can selectively inhibit microbial topoisomerase and DNA cyclase in the prevention and treatment of infectious diseases, and effectively inhibit the replication and expression of bacterial genes (Kocsis *et al.,* 2016). They have high utilization rate and wide application range.

However, with its extensive clinical application, the incidence of adverse reactions increased accordingly (Ganswindt *et al.,* 2003). Survey data show that among the adverse reactions caused by quinolones, adverse reactions of central nervous system can account for more than 12%, significantly higher than other types of antibiotics (Badhan *et al.,* 2014). In this paper, 70 patients with adverse reactions of central nervous system during the use of fluoroquinolones in our hospital were studied. The incidence of adverse reactions was retrospectively analyzed and the influencing factors were analyzed.

MATERIALS AND METHODS

Research objects

70 patients admitted to a hospital in Jinan from January 2016 to June 2017 were selected as the study subjects. During the use of fluoroquinolones, the patients had adverse reactions to the central nervous system. All patients met the criteria for screening adverse drug reactions (ADRs) formulated by the Ministry of Health. Among them, 38 were males and 32 were females. The age of patients ranged from 21 to 75 years, with an

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average age of (51.9±2.5) years. All patients were approved by ethics committee of our hospital, ethical approval number as 2015AHSUT2 and all patients signed on the informed consent. Retrospective analysis of adverse reactions in patients, including the main manifestations, degree of adverse reactions, the route of administration, the way of administration, whether patients have neurological diseases, etc.

Mechanism of action of fluoroquinolones

Fluoroquinolones have strong selectivity, which can inhibit both topoisomerase and DNA cyclase in bacteria, thus interrupting the continued synthesis and repair of bacterial DNA, and killing bacteria in active and static stages. Fluoroquinolones have selective effects on the molecular helix structure of bacteria, but have no effect on humans (Marchant, 2018).

Pharmacokinetics

When fluoroquinolones are taken orally on an empty stomach, the dosage is about 35% (Marcianes *et al.*, 2017). They are further dispersed in liver, kidney, lung, uterus, prostate and sputum, urine, blood and other body fluids. The plasma half-life of serum protein is about 3.5 hours, and its binding rate is about 12.5% (Millspaugh *et al.*, 1996; Manera *et al.*, 2015). If the renal function is abnormal, its half-life can be prolonged to about 2.5 hours. In blood concentration, 1 oral doses of 0.4g or 0.8 g can achieve peak value. When administered intravenously, the drug concentration maintains a high value in urinary, digestive, reproductive and other tissues, and can also infiltrate into prostate, bone and brain tissues.

Adverse reactions of fluoroquinolones

The molecular junctions of quinolones not only determine their antimicrobial activity, but also are closely related to their ADR. The main parent structures are quinolone nucleus and 1,8-naphthodinone nucleus. The common points are l-N, 3-carboxyl and 4-carbonyl. The introduction of fluorine atoms at 6 sites is called quinolones, which increases the antimicrobial activity and can connect different substituent groups at other sites. The interaction and reproductive toxicity of 1-position-controlled quinolones with theophylline; 3-position carboxyl group and 4-position carbonyl group are related to the chelation of FOs and metal ions and can bind to Mg2+, Ca2+, etc. 5-position and 8-Position substituents determine the phototoxicity of FQ. Position determine adverse drug reactions in the central nervous system. In addition, seven sites also involve the interaction of drugs with theophylline and non-steroidal resistance (NSAIDs).

Some studies suggest that the adverse reactions of central nervous system may be that quinolones and their metabolic products compete with GABA, a central inhibitory neurotransmitter, which inhibits GABA activity and increases the excitability of central nervous system, leading to convulsions and epilepsy. It has been found that quinolones with 7 piperazine cycles have similar structures to GABA receptor antagonists, which can make them have a strong affinity for GABA in the brain and antagonize GABA receptors to produce central nervous system symptoms. The antagonism of quinolones to GABA depends on the structure of 7-heterocyclic substituents. By methylation, the space volume of substituents is increased. Compared with 7-piperazine-substituted quinolones, the antagonism of 7-methylpiperazine-substituted quinolones GABA is obviously weakened and the toxicity is reduced.

STATISTICAL ANALYSIS

The experimental data were analyzed by SPSS12.0 software. The counting data were expressed as "n, %" and compared with chi-square test, the difference was statistically significant with $P<0.05$.

RESULTS

Basic situation

The main adverse reactions of 70 patients were observed. 42 patients with mild adverse reactions had dizziness, irritability, insomnia, tinnitus, insomnia and general fatigue as the main symptoms, while 28 patients with moderate and severe adverse reactions had neuropsychiatric symptoms such as anxiety, depression, nervous excitement, hallucination and optic hallucination. Severe organ or system damage 54 patients could recover by themselves after withdrawal without intervention The remaining 8 patients were treated with diazepam or lumina, 2 cases recovered, 12 cases improved, and 1 case had mild sequelae

Incidence of adverse reactions

Retrospective analysis of the incidence of adverse reactions in patients of different gender and age groups showed that there was no significant difference in the proportion of male patients and female patients ($P>0.05$), but the proportion of adverse reactions in elderly patients over 60 years old was significantly higher than that in patients under 60 years old ($P<0.05$), as shown in table 1.

Among 35 patients with adverse reactions of central nervous system, the proportion of intravenous drug users (82.85%) was significantly higher than that of other drug delivery routes, while the proportion of combined drug users (74.29%) was significantly higher than that of quinolones alone (25.71%). There were significant differences between the two groups ($P<0.05$), as shown in table 2. As shown in table 3, the proportion of adverse reactions caused by intravenous fluoroquinolones was the highest (58.7%) and the lowest (8.7%) was intravenous fluoroquinolones.

Table 1: Relationship between age, sex and incidence of adverse reactions

Basic information		Case	Proportion%
Sex	male	38	54.29
	female	32	45.71
Age	≥60	46	65.71
	<60	24	34.29

Table 2: Route of administration, mode of administration and incidence of adverse reactions

Drug delivery		cases	Constituent ratio (%)
Route of administration	Intravenous administration	29	82. 85%
	Oral administration	4	11. 43%
	Other	2	5. 71%
Drug delivery	use separately	9	25. 71%
	Combined use	26	74. 29%

Table 3: Adverse reactions to different routes of administration

Adverse reaction pathways	cases	Constituent ratio (%)
Orally	30	42.9
intravenous injection	8	11.4
Intravenous drip	32	45. 7

Table 4: History of neurological disorders in patients

History of nervous system diseases	cases	Incidence rate (%)	Type of disease	cases
Had a history of illness	19	27.14	epilepsy	8
			Arteriosclerosis	4
			Parkinson syndrome	3
			brain tumor	4
No history of disease	52	74.4		

Table 5: Distribution of drugs causing central nervous system adverse reactions

Drug name	cases	Constituent ratio (%)
Levofloxacin	38	54.28
ciprofloxacin	15	21.42
Moxifloxacin	7	10.0
gatifloxacin	4	5.7
Ofloxacin	2	2.8
Lomefloxacin	2	2.8
fleroxacin	2	2.8

Distribution of adverse drug

Of the patients, 19 had a history of neurological diseases (27.14%), including 8 epilepsy patients, 4 cerebral arteriosclerosis patients, 3 Parkinson's syndrome patients and 4 brain tumors patients, as shown in table 4. In this survey, there were 7 kinds of adverse drug reactions, of which 31 cases were caused by levofloxacin, accounting for 44.28%. The other types of adverse drug reactions were listed in table 5.

DISCUSSION

Fluoroquinolones are a class of all-synthetic antibiotics with broad antimicrobial spectrum, strong activity, good stability, long half-life, high bioavailability, good oral absorption effect and high tissue concentration in clinical treatment (Mcdonald, 1980; Nau *et al.,* 2018). Common floxacin drugs, such as moxifloxacin, ciprofloxacin, pefloxacin, ofloxacin, levofloxacin, etc. Ofloxacin and enoxacin are widely used in clinical practice (Ostojic *et al.,* 2015). Studies have found that there is a high incidence of adverse reactions in the central nervous system in the use of fluoroquinolones, such as fleroxacin (Pupo *et al.,* 2017). The incidence of adverse reactions in the central nervous system is as high as 70% (Saganuwan, 2017). It has been forbidden to use levofloxacin. Even

levofloxacin, which has a relatively low incidence of adverse reactions in the central nervous system, has a incidence of 0.2%-1.1% (Samyde *et al.,* 2016). Adverse reactions showed dizziness, headache, vertigo, fatigue, depression, restlessness, nervous excitation, insomnia and other symptoms, the serious can develop into severe mental disorders (Shi *et al.,* 2015). In this paper, 70 patients with adverse reactions of the central nervous system were reported. Most of them recovered or improved after withdrawal without intervention. Most patients with neuropsychiatric symptoms could obtain good prognosis through drug intervention such as diazepam.

The main fluoroquinolones causing adverse reactions were levofloxacin. The possibility of adverse reactions was higher when intravenous drip was administered. The adverse reactions mainly involved nervous system. Clinicians should not only pay attention to their antimicrobial effects, but also strictly grasp the indications of drugs to avoid adverse consequences (Vidadala *et al.,* 2016). The results showed that the proportion of intravenous drip was the highest (62.7%) in the reports of adverse reactions related to fluoroquinolones (Sun *et al.,* 2015). Therefore, fasting before intravenous drip should not be used and low speed should be reasonably controlled in the process of drip in order to avoid adverse reactions. For intravenous drip, we should control the dripping speed reasonably. The main adverse reactions of fluoroquinolones are neurological symptoms. This may be due to the fact that fluoroquinolones are liposoluble and can enter brain tissue through blood-brain barrier, inhibiting the excitation of central nervous system caused by the combination of GABA and receptors (Wasser *et al.,* 2000). Therefore, the incidence of adverse reactions of nervous system is high.

The related factors were analyzed. It can be seen that age, intravenous administration, drug combination and past history of neurological diseases are the main factors leading to adverse reactions in the central nervous system (Wingfield *et al.,* 2001). This is due to the decline of renal function and the prolongation of half-life of drugs with age, which lead to drug retention in the blood and affect the central nervous system. However, intravenous administration of quinolones can cause adverse effects on patients because of its fast entry into the blood and short time of complete metabolism of drugs. At the same time, when quinolones are used in combination with theophylline, NSAIDs, carbamazepine or metal-rich drugs, adverse events should occur. When applied to patients with a history of neurological diseases, the decrease of plasma protein content may lead to the destruction of blood-brain barrier, the increase of drug content in brain tissue fluid and the increase of the incidence of adverse reactions. In conclusion, in the course of fluoroquinolones treatment, it is possible to induce adverse reactions in the central nervous system due to older age, intravenous administration, drug combination and previous neurological diseases.

Influencing factors of central nervous system adverse reactions of fluoroquinolones

Age: Adverse reactions of central nervous system of quinolones can occur in any age group. FQ reported in the literature. Drug ADR is related to the age of the elderly and tends to increase with the increase of the year. It may be due to different degrees of impaired liver and kidney function in the elderly patients, slow drug metabolism and easy accumulation. The incidence of cerebral atrophy or cerebral atherosclerosis, poor tolerance and low plasma protein content is higher.

Past History: Older patients with previous neurological diseases such as epilepsy, Parkinson's syndrome, cerebral arteriosclerosis, brain tumors, etc. suffered from the decrease of plasma protein content and the ability of plasma protein to bind to drugs, and the blood-brain barrier was destroyed due to their psychological state. Drug concentration in brain tissue fluid increased, and the incidence of adverse reactions. Increase significantly

Renal function: Quinolones are excreted mainly through the kidney. Most of them are excreted by the original urine of drugs. The clearance rate of patients with renal insufficiency decreases (Zhang, 2015). The clearance half-life is long. It is easy to lead to drug accumulation. The blood concentration of quinolones rises. Thus, the central nervous system does not respond. Therefore, patients with renal dysfunction, especially elderly patients, should be avoided, and should be used according to the degree of impaired renal function (Nau *et al.,* 2018). Individualized adjustments of dosage and interval of administration should be made to avoid large doses even in patients with normal renal function, so as to avoid crystallization urine and renal failure, and renal function and symptoms should be monitored when drugs with greater nephrotoxicity are used.

Dosage, route and combined medication:It was found that dosage was a risk factor for adverse reactions of the central nervous system, and the degree of response was positively correlated with dosage (Mcdonald, 1980). Intravenous drug use was more likely to cause ADR of the nervous system than oral and local drug use, which might be related to the rapid increase of blood drug concentration during intravenous drug use, and the decline of renal function, drug elimination ability and elimination time in the elderly (Sun *et al.,* 2015).

Prevention and treatment of central nervous system adverse reactions by fluoroquinolones

Strict indications: The old patients with renal insufficiency, nervous system diseases and senile patients are more likely to suffer from serious ADR of central

nervous system (Wasser *et al.,* 2000). Therefore, the indications and contraindications should be strictly controlled. For those patients with previous epilepsy, Parkinson's disease, psychiatric history or family psychiatric history, the use of this drug should be avoided as far as possible, and other drugs that are not easy to penetrate the blood-brain barrier should be selected(Wingfield *et al.,* 2001). In order to avoid inducing severe psychiatric symptoms, patients with renal dysfunction, especially the elderly, should use as little as possible or cautiously as possible, formulate reasonable dosage regimens according to the patient's body condition, adjust dosage and time of administration, closely observe the occurrence of adverse reactions of the central nervous system. Once neuropsychiatric symptoms are found, drugs should be stopped immediately. If necessary, appropriate symptomatic treatment should also be given (Samyde *et al.*, 2016). Pregnancy should be used with caution or prohibition of the drug, breast-feeding women must avoid breast-feeding. infants and young children because of the imperfect development of blood-brain barrier, drugs easy to enter the central nervous system and produce corresponding toxic symptoms, should be avoided as far as possible.

Pay attention to drug interactions: For the patients who are using theophylline, NSAIDs and carbamazepine, the use of quinolones should be cautious and avoided as much as possible. If necessary, the dosage of theophylline should be adjusted and the concentration of theophylline in blood should be closely monitored. Drugs are used together so as not to induce neuropsychiatric symptoms.

CONCLUSION

In the course of clinical application of fluoroquinolones, physicians should strictly follow the principles of clinical application of antibiotics, strictly grasp the indications and routes of administration, pay attention to the dosage and course of treatment, and strengthen the observation and monitoring of adverse reactions in the course of administration in order to prevent the occurrence of adverse reactions. At the same time, laboratory monitoring should be strengthened, antibiotics management should be strengthened, abuse prevention should be strengthened, relevant professional training of medical staff should be strengthened, awareness of adverse drug reactions should be raised, rational drug use awareness should be enhanced, and drug safety should be ensured. In addition, the analysis of antimicrobial spectrum and drug resistance of quinolones should be done in the course of their application, and the occurrence of adverse reactions should be effectively prevented and controlled by phased drug use.

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