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Clinical pharmacist intervention in contraindications of the co-administration of cefoperazone and ambroxol hydrochloride injection

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Abstract. – BACKGROUND: Clinical pharmacists identified contraindications in two cases concerning the co-administration of cefoperazone and ambroxol hydrochloride injection, prompting a thorough investigation.

CASE PRESENTATION: Clinically, two cases of contraindications for the co-administration of cefoperazone and ambroxol hydrochloride injection were discovered. After the intervention and analysis by clinical pharmacists, the possible reason could be the precipitation of free alkali due to the immediate administration of ambroxol after the infusion of cefoperazone. Clinical pharmacists suggested avoiding the co-administration of the two and recommended flushing the intravenous lines with 5% glucose injection or 0.9% sodium chloride injection during intravenous infusion to prevent direct drug interaction causing precipitation, thereby reducing the occurrence of adverse events. No adverse events occurred after the intervention, and no harm was caused to the patients.

CONCLUSIONS: The co-administration of cefoperazone and ambroxol hydrochloride injection can lead to the precipitation of free alkali, posing a risk of adverse events. Clinical pharmacists' intervention could prevent this interaction. This practice has been shown to be effective, with no subsequent adverse events reported.

Key Words:

Cefoperazone Injection, Ambroxol Hydrochloride Injection, Contraindications, Clinical Pharmacist, Intervention.

Background

Ambroxol hydrochloride injection, as an active metabolite of bromhexine, has the functions of dissolving, secreting, and promoting the excretion of mucus. It can effectively promote the expulsion of thick respiratory secretions, improving the patient's respiratory conditions[1,2]. Clinically, it is mainly used for acute and chronic pulmonary diseases with abnormal sputum secretion and poor sputum expulsion[3,4]. Cefoperazone injection is a third-generation cephalosporin antimicrobial favored by clinicians due to its broad antimicrobial spectrum and stability against beta-lactamase[5-7]. It is often used alternately or mixed with other drugs, mainly for infections caused by sensitive bacteria, such as pharyngitis, tonsillitis, acute and chronic bronchitis, pneumonia, pyogenic lung disease, pyelonephritis, cystitis, prostatitis, meningitis, and gynecological infections[8-12].

With the outbreak of the COVID-19 pandemic, it is necessary to consider treating the combined bacterial infection with antibiotics[13-15]. For example, after being infected with the COVID-19 virus, local respiratory mucosal damage and immune function may be impaired, possibly leading to secondary bacterial infection. This situation is more common in the elderly and people with underlying diseases. Currently, these two drugs are commonly used in clinical practice, and their combined use is very prevalent. The authors found two cases of contraindications for the co-administration of cefoperazone and ambroxol hydrochloride injection, which are reported as follows.

Case Report

Case 1

A male, 79 years old, was diagnosed with bacterial pneumonia on April 9, 2023. On April

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10, the patient had a fever of 38.3°C, occasional coughing, and expectoration. He was prescribed intravenous cefoperazone 2 g+100 ml sodium chloride injection as per doctor's advice. On April 19, after the patient was infused with cefoperazone, and 15 mg of ambroxol hydrochloride injection was pushed into the intravenous infusion channel; the nurse noticed a white flocculent substance in the intravenous infusion channel and immediately stopped the infusion and consulted a clinical pharmacist. After the intervention of the clinical pharmacist, the patient was given an oral ambroxol hydrochloride solution for expectoration treatment.

Case 2

A male, 73 years old, was diagnosed with bacterial pneumonia on April 18, 2023. On April 19, the patient was given intravenous cefoperazone 2 g+100 ml sodium chloride injection as per doctor's advice. After the infusion of cefoperazone, 15 mg of ambroxol hydrochloride injection and 10 ml of 0.9% sodium chloride injection were pushed into the intravenous channel. The nurse noticed a white flocculent substance in the tubing, immediately stopped the infusion, and consulted a clinical pharmacist. After the intervention by the clinical pharmacist, the patient was given oral ambroxol tablets for expectoration treatment.

Analysis of Clinical Pharmacist Intervention

The clinical pharmacist first ruled out quality issues during the infusion of the two drugs and confirmed that the abnormal precipitation in both cases was not due to mixing with other drugs. Checking the instructions, no contraindications for the combination of the two drugs were found. After careful verification by the clinical pharmacist, it was found that studies[1] showed that white turbidity appears immediately after mixing 1 ml of ambroxol hydrochloride injection, 0.25 g of cefoperazone sodium, and 10 ml of 0.9% sodium chloride solution.

The clinical pharmacist analyzed that the possible reason for the precipitation in both cases was that after the infusion of cefoperazone, there was still some residual fluid in the intravenous channel. Immediately following this, ambroxol hydrochloride injection was infused, which was mixed with the residual cefoperazone in the intravenous channel to produce precipitation.

Ambroxol hydrochloride injection is a trans-4-cyclohexanol hydrochloride with a pH of 5.0. When mixed with an injection with a higher pH, it can destroy the stability of the drug and produce free alkali, resulting in white turbidity or white flocculent precipitation. The precipitate is very likely to be free alkali of ambroxol or its complex[16].

Suggestions of Clinical Pharmacist

According to the clinical pharmacist, the instructions for ambroxol hydrochloride injection describe that the combination of ambroxol hydrochloride and antibiotics can increase the concentration of antibiotics in lung tissue. It is recommended to add an appropriate amount of 5% glucose injection or 0.9% sodium chloride injection to flush the intravenous line between the two infusions. This lengthens the interval between the administration of different drugs, avoids direct drug interactions that can cause drug precipitation or turbidity, impacts the drug's effectiveness, and leads to adverse reactions[17].

Studies[18,19] have found that many drugs may be incompatible with ambroxol hydrochloride injection, most of which are commonly used drugs in respiratory medicine. In clinical treatment, it is very likely that ambroxol hydrochloride injection will be combined with these drugs. When using ambroxol hydrochloride injection with various types of drugs to treat diseases, it is necessary to strictly control the pH of the mixed solution to avoid mixing with drugs that can make the pH of the mixed drug solution >6.3, to prevent the impact on the drug effect and the precipitation of drugs. Therefore, it is suggested that compatibility tests of ambroxol hydrochloride injection, cefoperazone injection, and other commonly used injectables in clinical practice can be conducted. The compatibility test comprehensively examines the appearance of the drug solution after mixing, changes in pH value, drug content, and the number of micro-particles in the solution.

Conclusions

In conclusion, this report highlights the potential for precipitation and incompatibility when cefoperazone and ambroxol are co-administered intravenously without flushing the IV line in between. The intervention of clinical pharmacists prevented patient harm in these cases. However, the occurrence of two cases in a short time frame indicates this is likely an underrecognized interaction that should be better characterized. Fur-

ther research is needed to clarify the mechanism and determine best practices for administration. In the interim, pharmacists and nurses should be alert for signs of incompatibility and proactively flush IV lines between cefoperazone and ambroxol. Hospitals may consider modifying order sets and infusion protocols. Adverse events should be reported to improve product labeling. Increased awareness and precautions have the potential to avoid medication errors and enhance patient safety with these commonly used respiratory drugs.

Ethics Approval

This study was approved by the Ethics Committee of Wuxi Mental Health Centre, with the grant number WXMHCIR-B2020LLky053.

Informed Consent

Written informed consent was obtained from the patients. All methods were performed in accordance with relevant guidelines and regulations. The patients understood the report and signed the consent to publish the case details without disclosing privacy.

Availability of Data and Materials

The dataset generated during and analyzed during the current study is available from the corresponding author upon reasonable request.

Conflict of Interests

The authors declare no conflicts of interest.

Authors' Contributions

Zhiqiang Du and Haohao Zhu conceived the study; Zhiqiang Du, Qin Zhou, Yuan Shen, Rongrong Lu and Ying Jiang collected the report; Ying Jiang and Haohao Zhu wrote the manuscript; and Haohao Zhu edited the manuscript.

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