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Examination and Thinking Caused by Leucin A Injection Incident

Haiyang Sun, Xinyuan Chen, Hongxia Li

North China University of Science and Technology School of Pharmacy, Tangshan, Hebei 063210, China

Abstract

Problem drugs refer to drugs that meet the requirements according to the approved drug standards, but are clinically abnormal. Review and analysis of the inspection process of the second drug Leupococcus A injection event，The general process of analysis and inspection of problematic drugs in our country at the present stage is discussed，The steps of comprehensive analysis, precise analysis and scientific conclusion should be used for routine inspection and scientific conclusion for the drug in question.

Keywords

Leucin A Injection Incident; Diethylene Glycol; Toxicity; Excipients Rational Drug Use.

1. Event Introduction

On April 22 and 23, 2006, two patients with severe hepatitis in the Department of Infectious Diseases of the Third Hospital of Zhongshan,Guangzhou suddenly developed symptoms of acute renal failure. On the 29th and 30th, another patient continued to have the symptoms. Through investigation, the hospital focused on the "Leucin A Injection" produced by Qiqihar Second Pharmaceutical Co., Ltd. (hereinafter referred to as Qi Eryao), which is the only drug that patients have used that day.

On May 2, the hospital basically determined that the incident was indeed caused by leucine a injection. Report, seizure, investigation and inspection. The State Food and drug administration, the national adverse drug reaction monitoring center, Heilongjiang Provincial Bureau, Guangdong Provincial Bureau, Guangdong Provincial Institute for drug control and other units quickly entered the battle. On May 4, the inspection results of Guangdong Institute for drug control showed that the product in question met the requirements according to the national drug standards. However, in the experiment compared with the leucine a injection produced by Yunnan Dali Pharmaceutical Co., Ltd., the UV spectrum of leucine a injection produced by Qi eryao has an absorption peak at 235 nm; In the acute toxicity pre test, the toxicity of leucine a injection produced by Qi eryao was significantly higher than that produced by Dali pharmaceutical. The leucine a injection of Qi Er Yao was confirmed to contain up to 30% diethylene glycol by liquid chromatography-mass spectrometry, gas chromatography and infrared spectroscopy. Diethylene glycol will be oxidized into oxalic acid in the body, resulting in renal damage and acute renal failure. Normal drugs should not contain this component. Why does high concentration diethylene glycol appear in leucine a injection of Qi eryao?

After investigation, the solvent propylene glycol required for the production of leucine a injection was purchased by Niu Zhongren, a purchaser of Qi eryao, from Wang Guiping, an illegal businessman in Taixing City, Jiangsu Province. Wang Guiping forged the product registration certificate and other certificates and sold the industrial raw material diethylene glycol to Qi eryao in the name of Taixing Chemical Plant of China Geology and Mining Corporation in October 2005. After the fake raw materials entered the factory, Chen Guifen, director of the laboratory, and others seriously violated the operating procedures, failed to

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compare and identify the test atlas with the standard atlas, changed the relative density of the test sample to the normal value and issued the certificate of conformity when it was found that the relative density of the test sample was seriously inconsistent with the standard. As a result, fake excipients were put into production, the poison "leucine a injection" was manufactured and put into the market, which eventually led to the tragedy of 13 deaths and kidney toxicity of some people.

2. Acute and Chronic Toxicity of Diethylene Glycol

Diethylene glycol is a low toxic chemical substance. Due to its rapid metabolism and no obvious accumulation after entering the human body, no evidence of carcinogenic, teratogenic and mutagenic effects has been found so far, but high-dose intake will damage the kidney. Diethylene glycol can be rapidly absorbed by oral administration and discharged from urine, and the absorption of diethylene glycol by skin is less than 10% [1].

The oral LD species of diethylene glycol vary greatly [2]. The oral LD species of mice, rats, guinea pigs, rabbits, dogs and cats are 26.5, 16.6, 13.2, 26.9, 9.0 and 3.3g/kg respectively, of which cats are the most sensitive. Rats inhaled 4 400 mg / m3 diethylene glycol for 4 hours, and no animal died. Generally speaking, its acute toxicity is low. Diethylene glycol has no obvious irritation to skin mucosa and eyes. The long-term rat feeding experiment showed that giving the experimental animals a diet containing 1% diethylene glycol in 2 years would lead to slight growth retardation, a little calcium oxalate bladder stones, slight kidney injury and occasional liver injury; 4% diethylene glycol intake can cause increased mortality, significant growth rate retardation, bladder stones, and moderate to severe kidney damage. Male rats will have bladder tumors when exposed to large doses, most of which are benign. These tumors are related to the inflammation caused by bladder stones produced at large doses [3].

3. Mechanism of Diethylene Glycol Nephrotoxicity

The cause of diethylene glycol induced severe nephrotoxicity has not been clarified yet, but there is at least the following consensus: first, it is not caused by prototype, that is, parent drug, but by its metabolites; Secondly, the main metabolite is 2 (hydroxy) ethoxyacetic acid (HEAA), excluding glycolic acid, glycolaldehyde, glyoxal or calcium oxalate; Thirdly, HEAA damages not only kidney cells but also brain cells, but the detailed pathological mechanism is still unclear. Fortunately, it has recently been found that fomepizole, chemically named 4-methylpiperazole (4-mp), can be used as an antidote to diethylene glycol. Its mechanism is to inhibit liver enzymes and prevent the formation of HEAA, which is worthy of in-depth study. It is worth emphasizing that acetaminophen may have synergistic nephrotoxicity with diethylene glycol, because more than ten other preparations containing diethylene glycol used in Haiti have less acute renal failure.

The nephrotoxicity of diethylene glycol is generally reversible. After multi system monitoring support, such as mechanical ventilation, parenteral nutrition, rehydration and dialysis, children can survive.

4. How to Learn Lessons?

Woolf, a famous toxicologist of the poisoning control system in Massachusetts, USA, commented on the tragedy of diethylene glycol poisoning in Haiti, marveled that it was "a Darkwood revised" and called for no repetition of such a historical tragedy. Therefore, the author believes that the following problems should be urgently solved.

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4.1. Must Standardize the Production of Auxiliary Materials

Many people think that since it is an "auxiliary" material, it must be the supporting role of the preparation, so people have been watching the production of auxiliary materials for a long time. It is now recognized that many excipients also have adverse reactions, and individual can cause death. In the past, most of the above-mentioned more than ten kinds of auxiliary materials were produced by chemical reagent factories or chemical factories. Many varieties have no medicinal specifications for a long time. In clinical preparation, only chemical reagents or chemical raw materials can be used to replace them. Although the selection level is very high (such as chromatographic pure reagents and guarantee grade reagents), they are all based on the requirements of laboratory (in vitro) tests No pharmacological and toxicological tests, such as sodium thiosulfate and sodium pyrosulfite; Commonly used buffer for pH adjustment, such as disodium hydrogen phosphate and sodium dihydrogen phosphate, as well as the most commonly used matrix polyethylene glycol, etc. Therefore, the state should promulgate the production specifications for pharmaceutical excipients as soon as possible, that is, formulate national quality standards (side by side with the Pharmacopoeia) and organize fixed-point production according to the production quality management specifications for pharmaceutical production (GMP) for short, so as to meet the needs of preparations and dispensing. [4]

4.2. Attach Great Importance to Ideology

The staff engaged in preparation and dispensing must not have a fluke mentality. They think that only a small amount of auxiliary materials are used in many dispensing and preparations, that is, it doesn't hurt to use some chemical reagents or chemical raw materials. If you want to know the opening of ideological understanding, the prepared agent must be produced.

4.3. The Manufacturer Shall Strictly Implement GMP

The manufacturer has passed GMP acceptance and certification. It does not mean that the batches of products produced meet the requirements of GMP, and the implementation of GMP is by no means superficial To make a fuss and deal with the inspection of the superior, we should start from bit by bit and pay constant attention to it. CMP has strict inspection regulations on raw materials, auxiliary materials and all packaging materials. Batch inspection must be carried out for incoming raw materials. It is also necessary to make it clear that non medicinal APIs are not used and really control the quality from the source.

The diethylene glycol incident once again sounded the alarm for the pharmaceutical industry. Human life is vital. We must not repeat the mistakes and let the tragedy of history repeat itself.

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