Letter to Editor

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Molecular pharmacovigilance: safety signal for drug modification

Abstract

Combined long term translational medical research and recent many years of pharmacovigilance practice, molecular pharmacovigilance concept is proposed to draw attention to molecular pharmacovigilance with the purpose of avoiding the situation in which the energy and time spent on pharmacovigilance practice ends up with a lot of paper works without touching the drug itself. Through pharmacovigilance practice, such as individual case safety report, aggregate report, and signal detection, causal relationship between serious adverse reaction and molecular group is established, using molecular techniques modify the molecular group directly to get rid of the adverse reaction and make safer medical products.

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To The Editor

Although there is more than 160 years history of pharmacovigilance[1] it is first time to raise the concept of molecular pharmacovigilance. Molecular pharmacovigilance is to identify causal relationship between adverse event and drug at molecular level and then, on the basis of such knowledge using molecular biological technique to modify the drug to get rid of adverse reaction. The significance of this concept is to connect signal detection, one of routine pharmacovigilance activities, and drug development activities, so that the signal detection activity not just ends up in labeling change, or ultimately in drug withdrawing from market, but may feedback to drug development, and results in direct molecular modification of the product and to produce safer medicine.

Objective

To introduce molecular biology (genetic engineering, biotechnology) into pharmacovigilance, to build two-way signaling between pharmacovigilance and drug development, to make safer medicinal products, especially safer biological (monoclonal antibody) and vaccine.

Background

From patient's perspective, in the aero of personalized medicine, attention is paid to how genetic makeup affects an individual's response to drugs, how genetic variation influences drug response in patients. Pharmacogenomics (combination of pharmacology and genomics) correlates gene expression or single-nucleotide polymorphisms with efficacy or toxicity of drug; from manufacturer's prospective, genetic engineering, also called genetic modification, is a molecular technique (biotechnology) which can directly manipulate a genome of an organism. New DNA may be inserted in the host genome by first isolating and copying the genetic material of interest, or by synthesizing the DNA, and then inserting this construct into the host organism. Insulin-producing bacteria were commercialized in 1982. As of September 2014, FDA already approved 46 diagnostic and therapeutic monoclonal antibodies, majority were produced with genetic engineering. It is the time to raise the concept of molecular pharmacovigilance.

Methods

Case studies. Case 1, poliovirus vaccine reverse mutation toxicity. Poliomyelitis (polio) is a crippling and potentially fatal infectious disease, which mainly affects young children. There is no cure for polio, it can only be prevented. Polio vaccine, given multiple times, can protect a child for life. There are 3 types of poliovirus, type I, type II, and type III. Type I vaccine is stable, but type II and type III vaccine are not so stable since there is reverse mutation related infection occurred during vaccination. Since type I vaccine is stable (no reverse mutation), which was strategically used as a vector, type II antigen encoding fragment (no reverse mutation) and type III antigen encoding fragment (no reverse mutation) was cloned into the vector, Type I/II and Type I/III chimera vaccines were generated, which can induce bivalent antibody in animals. Use same strategy multivalent vaccine type I/II/III can be produced. Safety signal (reverse mutation in this case) was directly used to guide modification to produce safer vaccine.[2] Case 2, HAMA (human anti-mouse antibody) response. Traditionally monoclonal antibody is produced in mouse, when used in human it can induce HAMA response, which not only decrease the effectiveness of the treatment, but also can cause life-threatening response, such as renal failure, in extreme case. Using humanized techniques can produce safer therapeutic antibody.[3]

Discussion

Molecular pharmacovigilance is proposed here. In molecular pharmacovigilance safety signal from pharmacovigilance practice can directly feedback to drug development to guide generation safer medicinal products by using molecular biology (genetic engineering, translational medicine). Hypothetically if a biological can cause anaphylaxis, the gene fragment encoding anti-allergic reaction peptide can be cloned into it; if a biological can cause neutropenia, the GM-CSF gene fragment can be cloned into it; for traditional chemical drug, if causal relationship is established between a chemical group and an adverse event, the chemical group can be modified to get rid of the adverse event. In addition, molecular pharmacovigilance can enrich pharmacovigilance methodology, for example, through data mining certain molecular structure can be linked to certain adverse event, or vise versus; molecular pharmacovigilance can mitigate the risk and ensure safety use of medicine, for example, biomarker anti –JCV antibody can be used to manage the risk of progressive multifocal leukoencephalopathy.

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Conflicts of Interest

There is no conflict of interest.

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