11. CURRENT TRENDS IN THE DEVELOPMENT OF ANTI-INFLUENZA DRUGS

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Introduction. In recent years, humanity has been facing one of the most dangerous diseases - Coronavirus, which has caused high morbidity and mortality. On 30 January 2020, WHO declared the COVID-19 outbreak a Public Health Emergency of International Concern. A number of treatment regimens were developed and each included anti-influenza drugs from neuraminidase inhibitors and a nucleoprotein inhibitor. Unfortunately, the RNA genome of influenza virus constantly mutates, which reduces the effectiveness of the drugs. There has been a need to develop new antiviral drugs.

Aim of study. To evaluate the current trends in the development of anti-influenza drugs.

Methods and materials. Electronic databases: Medline, Cochrane, Embase and Springer were accessed using "antiviral drugs", "influenza", "anti-influenza drugs" and "viral pandemics". Also, the search was conducted by using printed pharmaceutical and chemical journals. 112 bibliographic sources were eligible for our study.

Results. An increased interest in antiviral drugs has been highlighted during influenza pandemics, such as Spanish flu caused by H1N1 virus in 1918, Asian flu by H2N2 virus in 1957, Hong Kong flu by H3N2 virus in 1968, bird flu by H5N1 and H7N9 viruses in 2003 and 2013, respectively, as well as swine flu by H1N1 virus in 2009. Amantadine was the first anti-influenza drug, licensed in the 1960s and is a derivative of adamantine, which was used in influenza pandemics from 1957 and 1968. However, the use of adamantine antivirals has been limited in the past decade due to a high resistance developed by almost all influenza strains. From 1999-2000 became available neuraminidase inhibitors, which also are used in current medical treatment of A and B influenza. Until 2009 neuraminidase inhibitors were the only antiviral drugs, then a new class was developed - polymerase inhibitors. Antiviral drugs currently used in clinical practice of influenza have some disadvantages such as low lipophilicity and oral bioavailability (zanamivir < 5%). To solve the problems, some changes have been made in the chemical structure of antivirals: (1) esterification of carboxylic group to ester prodrugs improved the oral bioavailability (oseltamivir 35%), (2) esterification of highly hydrophilic guanidinium group and incorporating an aromatic moiety (1-hydroxy-2-naphthoic acid), (3) modification of the guanidine group to acylguanidine by attachment of lipophilic acyl substituent, (4) substitution of carboxylic group with bioisoesteres (hydroxamic acid, sulfinic acid, boronic acid).

Conclusion: New influenza strains and drug resistance, low lipophilicity and oral bioavailability of antiviral drugs continue to be the main problems in current therapy of influenza, which can be sort out by development of effective anti-influenza drugs, especially focusing on using congeners and conjugates of the existing neuraminidase inhibitors.