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The transdermal delivery efficacy of rimantadine under experimental influenza model in mice

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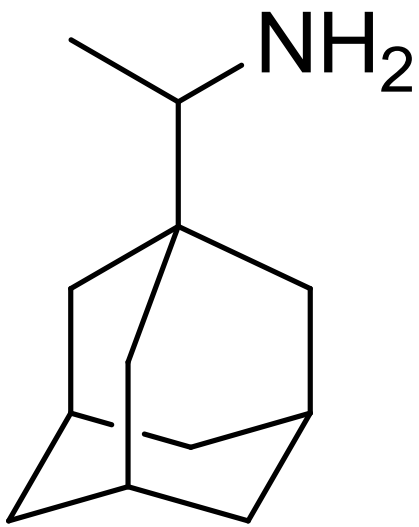


Abstract

Transdermal delivery of drugs is a novel method of pharmacotherapy for many diseases. The main advantages of this method of administration are

- prolongation of the drug action;
- absence of the drug concentration hopping;
- decrease of the side effect risk.

This method of administration has to be viewed for preventive actions and therapy of viral respiratory infections.

The aim of this work was studying the possibility of transdermal rimantadine delivery for influenza A prophylaxis and treatment in experimental animals. Rimantadine was administrated in the hydrogel matrix (formed from 1.2-propylene glycol and polyvinyl alcohol) in the doses 1 or 2 mg/mouse applied on the shaved back of mice 1 day before infection.

Mice of experimental and control groups were infected intranasally with highly pathogenic influenza virus A/PR/8/34 (H1N1). Challenge was carried out using 4 animals for each virus dilution within the range of 10^{-1} to 10^{-7}.

Deaths of animals were recorded for 14 days.

The results of our investigations had shown high anti-influenza efficacy of rimantadine under transdermal delivery. Differences of LD_{50} between control and experimental groups consist 1.7-1.75 $\log_{10}$ when dose of rimantadine was 1 mg/mouse and 2.25 $\log_{10}$ when preparation was administrated in dose 2mg/mouse.

In this study the anti-influenza efficacy of rimantadine after its transdermal administration was established for the first time.

Keywords: rimantadine, transdermal delivery, influenza

Introduction

During the last decade, transdermal delivery of drugs possessing the systemic action attracts much attention. Transdermal delivery of drugs is carried out by the help of transdermal therapeutic systems (TTS) – multilayer patches containing an active ingredient.

Transdermal delivery have some advantages, like: 1) it prolongs drug action, 2) it maintains drug concentration in the therapeutic range, 3) it doesn't hurt the patient, 4) removing TTS from the skin stops drug entering to the organism, 5) first-pass effect in the liver is reduced, 6) it enables use of drugs that exhibit a high activity but irritate the gastro-intestinal tract or have poor half-life time. Influenza viruses cause disease in patients of all ages, although the morbidity and mortality are highest among persons aged $\geq$ 65 years and persons of any age under medical conditions that place them at high risk for complications. Rimantadine hydrochloride is licensed for use in preventing and treating influenza A. However, rimantadine can cause CNS and gastrointestinal adverse reactions when administered orally to young healthy adults (e.g., insomnia, nervousness, anxiety, difficulty of concentration, light dizziness, nausea, vomiting, abdominal pain). Such reactions were reported with an incidence more than 1%. We hypothesized that low doses of rimantadine could constitute an efficient treatment when used in a TTS. Therefore we decided to study the transdermal rimantadine delivery effectiveness under experimental influenza in mice.

Methods

The experiments were performed on male mice weighing 18±2 g. The mice were kept under a continuous 12-h light-dark cycle at room temperature and provided with food and water libitum. Experimental protocols were approved by the Ethics Committee of the Pharmacological Committee of Ukraine and performed in strict accordance with the Ethics Committee regulations for the use of experimental animals.

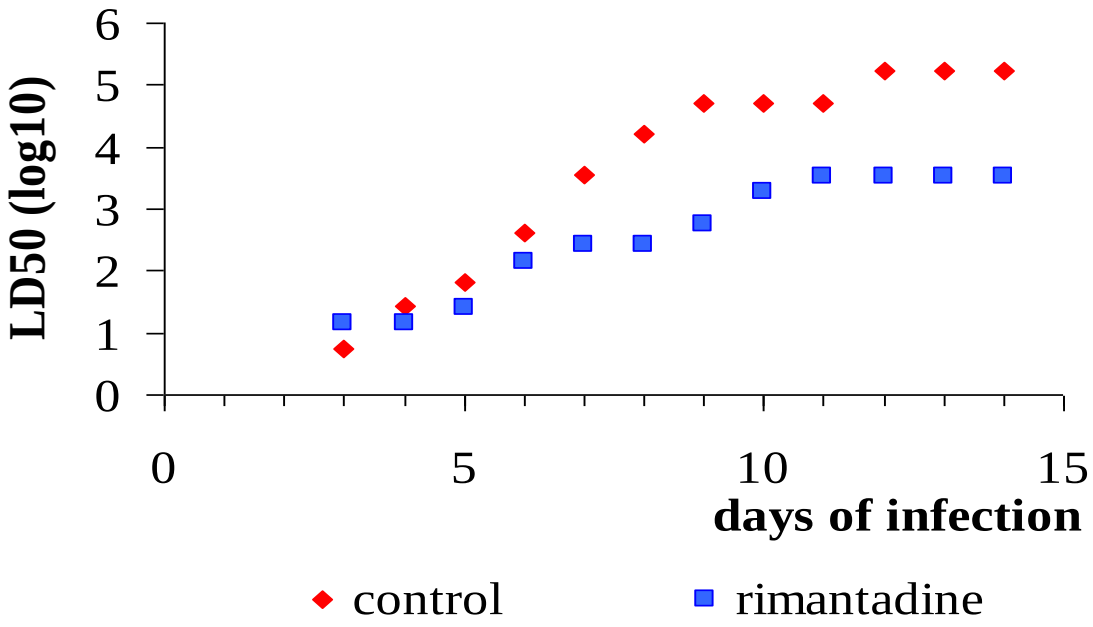
Applied transdermal system has adhesion hydrogel matrix (polyvinyl alcohol and 1.2-propylenglycol). It consists of base and plastificator, which improve the administration of active substance through the skin and do not induce irritation. TTS containing the rimantadine were applied on shaven backs of experimental animals (1 or 2 mg/mouse) and maintained there from 1 day before infection to the 10th day after infection. TTS without active substance were applied on shaven backs of control mice and maintained there during the same period.

Allantoic cultures of highly pathogenic influenza virus strain A/PR/8/34(H1N1) have been used for modeling infection in mice. Challenge was carried using 4 animals for each virus dilution within the range from 10^{-1} to 10^{-7} (V.Lozitsky et al., 1988). The mice were infected intranasally under light ether narcosis. Mortality of animals was recorded for 14 days. A 50% lethal dose (LD_{50}) was calculated with the use of modification of Kaerber method suggested by Ashmarin (I.Ashmarin, A.Vorobiov, 1962).

Results and discussion

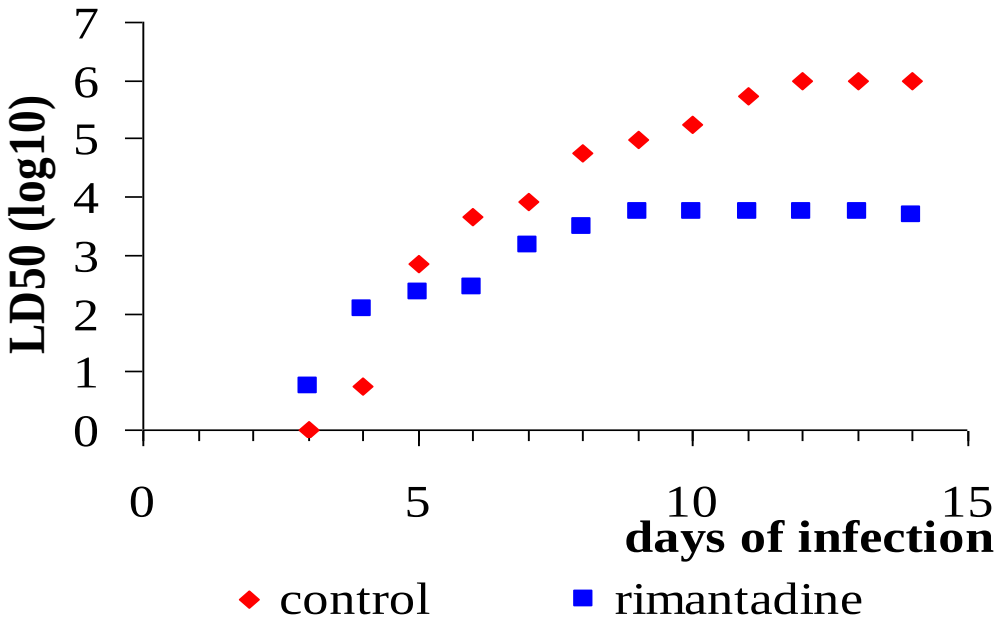
Results of our studies are shown in Figures 1 and 2. Rimantadine transdermal delivery was highly effective when the drug was administrated in both doses. But some differences took place. Differences of LD_{50} between control and experimental groups were more then 1.0 log_{10} on the 7th day and they were 1.7 log_{10} on the 14th day of experiment when dose of rimantadine was 1 mg/mouse (see Fig.1). Death of mice was not fixed in experimental groups after the 10th day when 1 mg/mouse of rimantadine was administrated and after the 9th day when the drug dose was 2 mg/mouse. Differences of LD_{50} between control and experimental groups were more then 1.0 log10 on the 6th day and they were 2.25 log_{10} on the 14th day of experiment when the dose of rimantadine was 2 mg/mouse (fig.1,2). So higher doses of rimantadine induced a higher level of anti-influenza effectiveness after its transdermal delivery.

Fig.1. Rimantadine transdermal delivery for treatment of experimental influenza (1 mg/mouse)



Differences of LD_{50} between control and experimental groups were more then 1.0 log_{10} on the 7th day and 1.7 log_{10} on the 14th day of experiment, when dose of rimantadine was 1 mg/mouse.

Fig.2. Rimantadine transdermal delivery for treatment of experimental influenza (2 mg/mouse)



Differences of LD_{50} between control and experimental groups were more than 1.0 log_{10} on the 6th day and 2.25 log_{10} on the 14th day of experiment, when dose of rimantadine was 2 mg/mouse

Conclusion

• In this study the anti-influenza efficacy of rimantadine after its transdermal delivery was established for the first time.

• Results of this study suggest good perspectives for anti-influenza agents transdermal delivery.

• Investigations in this direction are in progress.