

DOES THE UKRAIN PREPARATION PROTECT MICE AGAINST LETHAL DOSES OF BACTERIA?

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Summary: *Ukrain*, a semi-synthetic preparation obtained from *Chelidonium majus* L., is used in the treatment of cancer diseases. It has been observed to exert a protective influence in mice infected by influenza viruses. Recently, the influence of the preparation on the survival of mice infected by lethal doses of *E. coli* and *S. aureus* has been estimated. This preparation was administered to Balb/c mice subcutaneously in doses of 0.04, 0.4 and 4.0 mg/kg of body weight. *Ukrain* was given every second day during 20 days, or a short-term before-and-after method at 48, 24 and 2 h before the infection and or 2, 24 and 48 h after the infection of mice. The mice were infected intraperitoneally with *E. coli* or *S. aureus* in doses equivalent to 2LD₅₀. Increased survival of mice, depending on the dose of the preparation and the kind of infecting bacterium, was observed. The highest survival (50%) occurred in mice infected with *E. coli* and receiving the amount of the preparation corresponding to 0.4 mg/kg. The lowest survival was observed in mice infected by *S. aureus* and receiving the preparation in the amount of 4.0 mg/kg. Higher protective effectiveness of the *Ukrain* preparation was observed in mice when the preparation had been administered during 20 days as compared to the short-term before-and-after regime.

Introduction

Ukrain is a semi-synthetic preparation (alkaloid) obtained from the celandine *Chelidonium majus* and conjugated with thiophosphoric acid. This preparation is used in the treatment of cancer diseases (5, 7, 8, 11). It selectively acts on cancer cells but not the normal ones (5, 8). It is a preparation well tolerated by patients and not toxic (2, 14). One of its properties is to stimulate

the immune system (2, 4, 11, 14). It has been demonstrated to have a favourable influence on infections caused by influenza viruses (1, 3). This stimulation of the immune system, and protective action in experimental infections caused by influenza viruses, encouraged us to undertake studies to estimate the effectiveness of the above-mentioned preparation in experimental bacterial infections.

There is one question: does the preparation show protective action in mice infected by lethal doses of bacteria? The other question is the possible protective effect dependent on the dose of the preparation and the time of its administration.

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Materials and methods

Mice. The investigations were carried out on 10-12-weeks-old Balb/c mice, of both sexes and 24-32 g body weight. The mice were divided into several groups with 10 in each group (Table I). The sex distribution in the groups was similar and so was the weight distribution. The survival of mice was observed within 10 days starting from the infection time.

Ukrain preparation obtained from the firm Nowicky Pharma in Vienna was used subcutaneously in doses of 0.04 mg/kg, 0.4 mg/kg and 4.0 mg/kg of body weight. The preparation was used by two methods (Table I). The first method was based on the administration of the preparation every second day during 20 days (a total of 10 doses) before the animals were infected. In the

mice were infected intraperitoneally using a dose equivalent to 2LD₅₀.

Results

The Ukrain preparation had a favourable effect on the survival of mice infected by either *S. aureus* or *E. coli*. Its protective effect was dependent on the dose of the preparation and the species of infecting microorganism. The higher protective effectiveness was observed in mice infected by *E. coli*.

The highest survival (50%) was observed in the group of mice infected by *E. coli* which were treated for 20 days with Ukrain at 0.4 mg/kg (Fig. 1). A slightly lower survival (40%) occurred in the group which received a dose of 0.04 mg/kg ten

Table I Scheme of administering the Ukrain preparation

Preparation			Ukrain					
Time of administration			Every second day during 20 days			48h, 24 h, 2 h before infection and 2h, 24 h, 48 h after the infection		
Doses in mg/kg		0	0.4	0.04	4.0	0.04	0.4	4.0
Mice	not infected	X						
	infected by <i>E. coli</i>	X	X	X	X	X	X	X
	infected by <i>S. aureus</i>	X	X	X	X	X	X	X

X - Each group is composed of 10 Balb/c mice.

second method, the preparation was administered at 48, 24 and 2 hours before the infection and 2, 24 and 48 hours after the infection of the mice (a total of 6 doses).

Bacteria. The mice were infected either by *Staphylococcus aureus* of the «Smith» type or by a strain of *Escherichia coli* pathogenic for mice obtained from current clinical material. The infecting dose was established experimentally. The bacteria obtained from 18-hour cultures were suspended in a 2% solution of sterile gelatin. The

times in the 20 days. Short-term before-and-after infection administration of this preparation (the second method) induced a favourable effect (30% survival) at the dose of 0.04 mg/kg (Fig. 2). The other doses of the preparation used in this second method did not show favourable influence on the survival of animals, but in either of the methods they did not increase their mortality rate (Figs. 1, 2).

Lower survival than the preceding one was observed in the mice infected by *S. aureus*.

Protective effect of Ukrain against bacterial infections

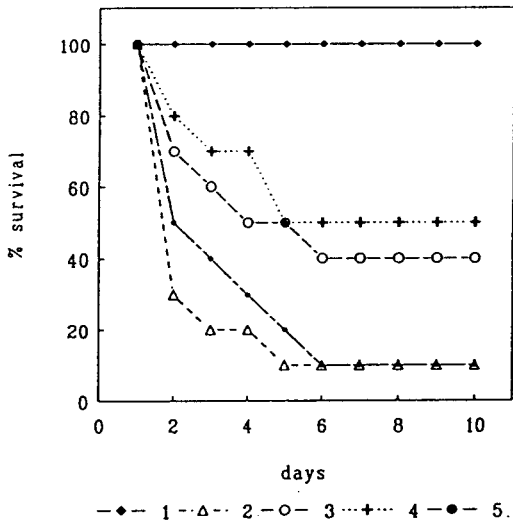


Fig. 1 Influence of Ukrain preparation administered every second day during 20 days on the survival of mice infected by *E. coli* (result in %).

1 - Control uninfected mice 3 - infected mice + Ukrain 0,04 mg/kg
2 - infected mice 4 - infected mice + Ukrain 0,4 mg/kg
5 - infected mice + Ukrain 4,0 mg/kg

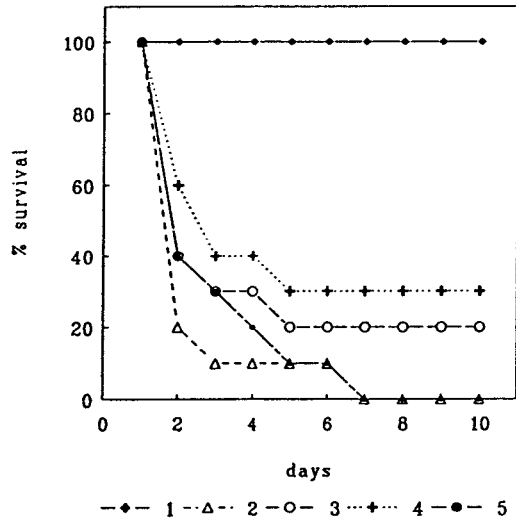


Fig. 3 Influence of Ukrain preparation administered every second day during 20 days on the survival of mice infected by *S. aureus* (result in %).

1 - Control uninfected mice 3 - infected mice + Ukrain 0,04 mg/kg
2 - infected mice 4 - infected mice + Ukrain 0,4 mg/kg
5 - infected mice + Ukrain 4,0 mg/kg

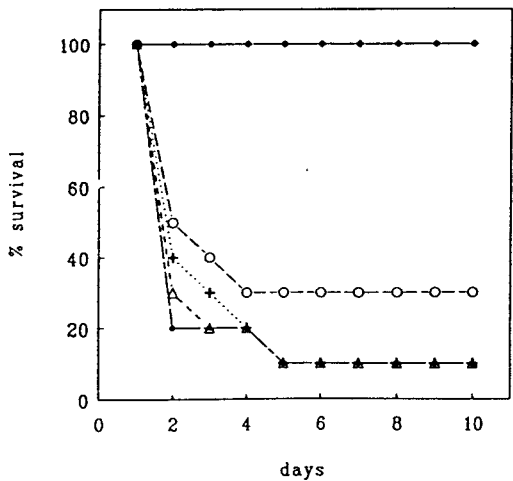


Fig. 2 Influence of Ukrain preparation administered 48h, 24h and 2h before infection and 2h, 14h and 48h after infection on the survival of mice infected by *E. coli* (result in %).

1 - Control uninfected mice 3 - infected mice + Ukrain 0,04 mg/kg
2 - infected mice 4 - infected mice + Ukrain 0,4 mg/kg
5 - infected mice + Ukrain 4,0 mg/kg

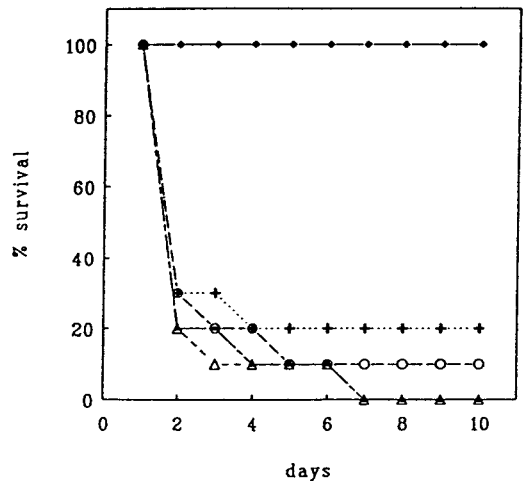


Fig. 4 Influence of Ukrain preparation administered 48h, 24h and 2h before infection and 2h, 14h and 48h after infection on the survival of mice infected by *S. aureus* (result in %).

1 - Control uninfected mice 3 - infected mice + Ukrain 0,04 mg/kg
2 - infected mice 4 - infected mice + Ukrain 0,4 mg/kg
5 - infected mice + Ukrain 4,0 mg/kg

Highest survival in this group of mice was 30% and occurred at the dose of 0.4 mg/kg over a period of 20 days (Fig. 3). The highest doses of the preparation, i.e. 4.0 mg/kg, did not show any favourable influence on the survival of mice. In general, higher protective effectiveness was observed when the preparation was administered over a 20-day period, as compared to the second method of short-term treatment (Fig. 4).

Discussion

Among the numerous publications on the Ukrain preparation and its anti-cancer properties it is hard to find any mention on the influence of the preparation on the course of infectious diseases (1, 3, 5, 6). The present paper is a continuation of a cycle of publications on this subject. Our previous observations relate to the influence of this preparation on the survival of mice infected by influenza viruses (1).

We also studied a direct inactivating influence of the preparation on influenza viruses and the bacteria of *S. aureus* and *E. coli*. The preparation did not show inactivating activity (unpublished results). We have recently estimated the protective influence of the preparation on the survival of mice infected by *E. coli* and *S. aureus*. In studying the dependence of the preparation dose and the kind of microorganisms involved, we observed a protective effect. Considering the stimulation of the immune system in the infections caused by influenza viruses and the data from the literature on the stimulating effect on selected parameters of the immune response, we think that the observed protective effect of the Ukrain preparation is also due to a stimulated immune system. In fact, the preparation increases the total number of T lymphocytes, T helper lymphocytes and the so-called natural killer (NK) cells (2, 10, 11).

Ukrain normalizes the relation of T helper to T suppressor lymphocytes and increases the concentration of complement constituents (7-9, 12, 14). Under the influence of the preparation it increases the activity of cytotoxic cells as well as

phagocytosis and the bactericidal properties of granulocytes and macrophages (6, 8, 12, 13).

The increased concentration of serum complement increases the opsonization of microorganisms by its constituents. These microorganisms are more readily phagocytized and killed by the phagocytizing cells. Increased survival of mice is also favoured by the increased activity of cytotoxic cells as well as by the general stimulation of the immune response by the preparation (5, 6, 8, 10).

Our investigation has introduced an additional practical aspect in the application of this preparation. The patients with neoplasms are rather often infected by different microorganisms. Such infections may be revealed before, and in the course of, treatment with the Ukrain preparation.

Our studies have shown that doses of the preparation being used act in a protective way in bacterial infections and do not increase the mortality of mice. One may use this preparation safely in patients with neoplasms in the course of infections. But it remains an open question whether there is a possible interaction of this preparation with antibiotics, used in the meantime before the treatment.

Answering the question contained in the title of this paper, one can say that the Ukrain preparation has a protective effect in experimental infections caused by the bacteria *E. coli* and *S. aureus*. This effect was especially evident at small doses of the preparation in long-term application.

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