DRUGS

THE ORIGINAL DOMESTIC DRUG OXOLIN: REFINED STRUCTURE OF THE DRUG AND SUMMARIZED EXPERIENCE OF OXOLIN OINTMENT USE IN MEDICINE

R. G. Glushkov,[1] T. A. Gus'kova,[1] I. S. Nikolaeva,[1] V. V. Peters,[1] K. F. Turchin,[1] O. S. Anisimova,[1] and E. V. Degterev[1]

Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 33, No. 9, pp. 47 – 53, September, 1999.

Original article submitted January 25, 1999.

INTRODUCTION

Influenza, as well as the other acute respiratory viral infections, are the most widespread viral infections that cause considerable damage to public health and economies all around the world. The permanent antigen variability of the respiratory viruses necessitates of using ethiotropic chemical drugs for the prophylaxis and treatment of these infections. In the past two decades, achievements in experimental and clinical virology, biochemistry of viruses, and organic chemistry allowed several effective antiviral preparations for systemic administration to be created and put into practice. These include arbidol, remantadin, adapromine, and deitiforin.

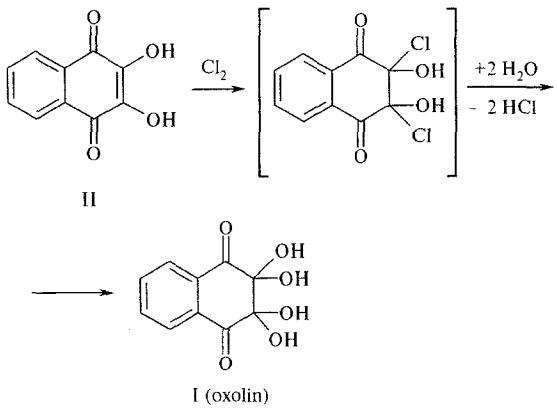
At the same time, taking into account the droplet character of spreading of respiratory infections and some features in the pathogenesis of these diseases, an important role in the prophylaxis and treatment of influenza and other acute respiratory viral infections belongs to preparations for local application. These remedies are frequently better tolerated and less toxic because of the absence of resorption effects.

The group of antiviral preparations for local application includes 0.25% oxolin ointment – a domestic remedy created and developed at the Center for Drug Chemistry – All-Russia Research Institute of Pharmaceutical Chemistry (Moscow). This ointment is used for the prophylaxis of influenza and for the treatment of catarrhal symptoms accompanying this disease [1].

A parent compound in the ointment is oxolin, which was originally assigned the structure of 1,2,3,4-tetrahydro-1,2,3,4-tetraoxonaphthalene dihydrate [1]. This is an odorless crystalline substance of white color, sometimes with a creamish tint, readily soluble in water. The aqueous solutions are unstable and darken in alkaline environment, being more stable in weakly acidic media.

OXOLIN STRUCTURE REFINED

Our structural investigations performed by the methods of mass spectrometry and NMR spectroscopy showed that oxolin molecules should be more correctly assigned the structure of 1,2,3,4-tetrahydro-1,4-dioxo-2,2,3,3-tetrahydroxynaphthalene (I). Taking into account the process of oxolin synthesis from isonaphthazarin (II), the general reaction pathway can be represented by the following scheme:



The proposed structure is confirmed by the following body of data.

The mass spectrum of oxolin measured by the method of chemical desorption ionization (Fig. 1) displays an intense peak of the quasimolecular ion MH^+ (m/z = 225 amu), as well as the peaks of $[MH–H_2O]^+$ (207) and $[MH–2OH]^+$ (191). Therefore, the molecular weight of compound I is greater by

[1] Center for Drug Chemistry – All-Russia Research Institute of Pharmaceutical Chemistry, Moscow, Russia.

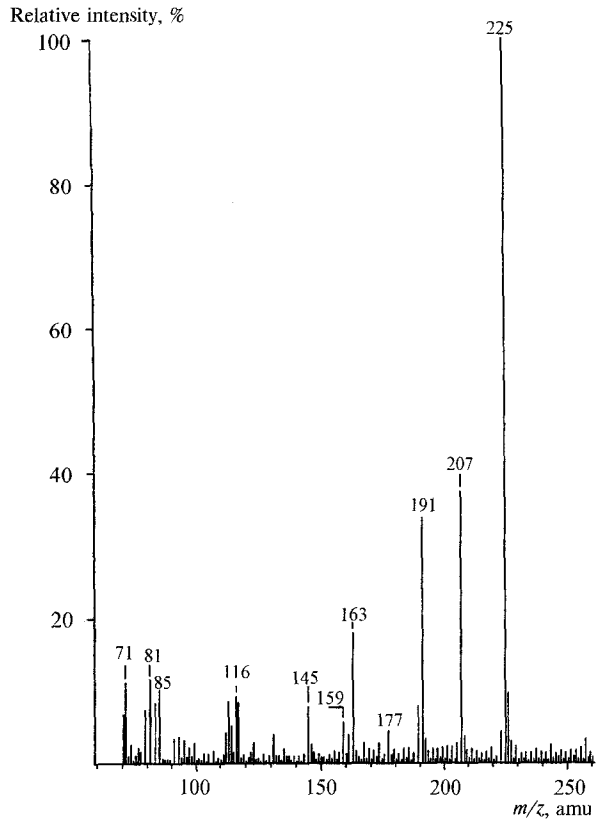


Fig. 1. Mass spectrum of oxolin measured by the method of chemical desorption ionization.

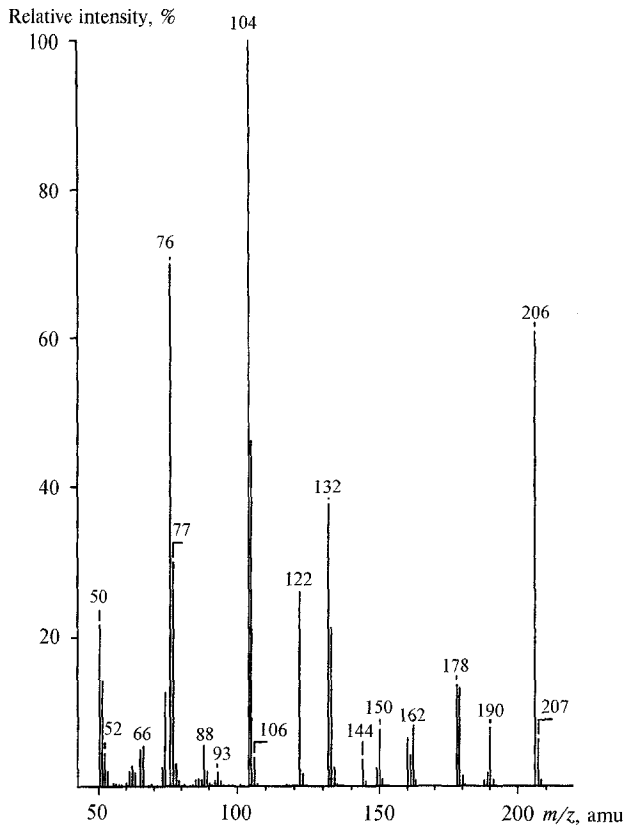


Fig. 2. Electron-impact ionization mass spectrum of oxolin.

36 amu than the value corresponding to 1,2,3,4-tetrahydro-1,2,3,4-tetraoxonaphthalene. This result suggests that oxolin possesses a tetraoxydiketone structure.

The electron-impact ionization mass spectrum of oxolin (Fig. 2) exhibits the peaks of $[M–H_2O]^+$ (206), $[M–2OH]^+$ (190), $[M–H–CO_2]^+$ (179), $[M–H_2O–CO]^+$ (178), $[M–H_2O–CO_2]^+$ (162), $[C_6H_4(CO_2)]^+$ (132), $[PhCOOH]^+$ (122), $[C_6H_4CO]^+$ (104), and $[C_6H_4]^+$ (76). This pattern of decay under the action of electron impact fully agrees with the proposed structure (I).

The ^1H NMR spectrum of oxolin (Fig. 3*a*) contains symmetric multiplets at $\delta = 8.00$ and 7.83 ppm belonging to the $H_{5(8)}$ and $H_{6(7)}$ protons, respectively (Fig. 3*b*), and a broad singlet at $\delta = 6.74$ ppm.[2] The intensity of the latter signal (4H units) is independent of the amount of water in the solvent, this water being represented by a signal in the region of $\delta = 3.3 – 3.4$ ppm. Therefore, the singlet at $\delta = 6.74$ ppm should be assigned to the protons of four equivalent OH groups in the proposed structure of I.

The ^{13}C NMR spectrum of oxolin contains signals at $\delta =$ 134.2 ($C_{6(7)}$), 126.9 ($C_{5(8)}$), and 133.7 ppm ($C_{4a(8a)}$), belonging to the equivalent pairs of carbon atoms in the benzene ring (Fig. 4*a*), and signals at $\delta = 193.6$ and 96.0 ppm. The signal at 193.6 ppm corresponds to two equivalent carbons of the carbonyl groups conjugated to the aromatic nucleus and, hence, occupying positions 1 and 4. The singlet at 96.0 ppm, which also belongs to a pair of equivalent carbon atoms, exhibits a considerable shift toward strong fields and, hence, cannot be assigned to carbonyl groups. Therefore, the tetraketone structure of oxolin must be rejected. Both the chemical shift and multiplicity of the latter signal are typical of an sp_3-hybridized quaternary carbon atom linked by δ-bonds to four neighbors – two carbons and two oxygens. This pattern corresponds to $C_{2(3)}$ in the refined oxolin structure proposed.

[2] Assignment of the ^1H NMR signals from benzene ring protons is given in the experimental physicochemical part below.

EXPERIMENTAL PHYSICOCHEMICAL PART

The experiments were performed with an oxolin sample of pharmacopoeial grade, meeting all the requirements of the corresponding pharmacopoeial clause (FS 42-1670 – 88).

The mass spectra of oxolin in the electron-impact ionization and the chemical desorption ionization modes were measured on a Finnigan SSQ-710 spectrometer (USA). The chemical desorption ionization mass spectra were obtained using isobutane as a reactive gas.

The NMR spectra were measured using a Varian Unity + 400 spectrometer (USA) operated at a working resonance frequency of 400 and 100 MHz on the ^1H and ^{13}C nuclei, respectively. The spectra were calibrated using signals of the

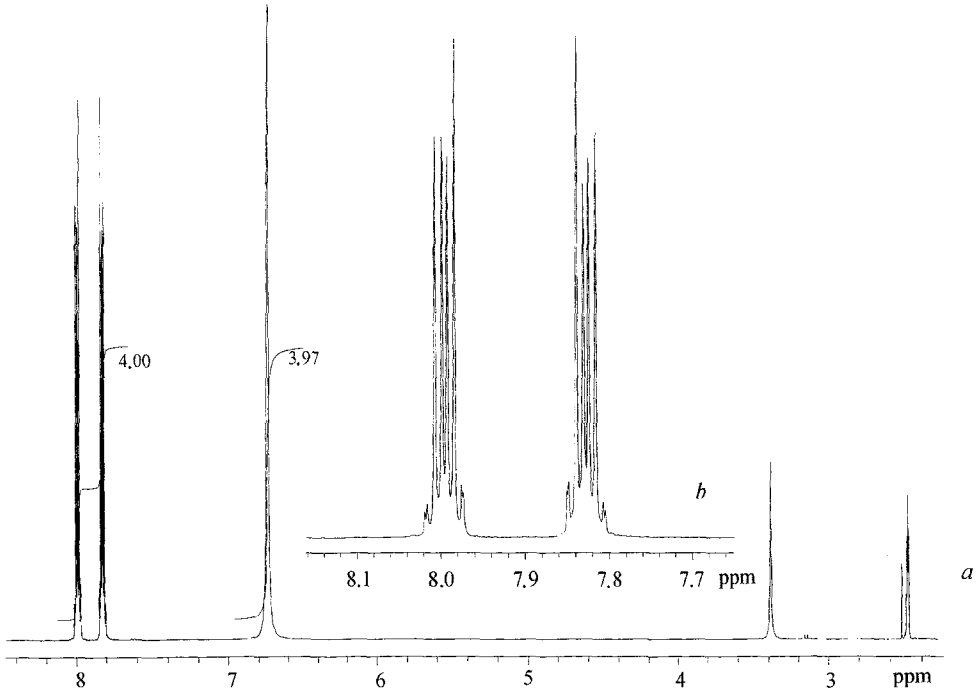


Fig. 3. ^{1}H NMR spectrum of oxolin in DMSO-d_6 (*a*); the signals from benzene ring protons recorded in an expanded scale (*b*).

DMSO-d_6 solvent as the internal standard with $\delta = 39.6$ and 2.49 ppm in the ^{13}C and ^{1}H modes, respectively.

The proposed assignment of signals from the benzene ring carbon atoms in the ^{13}C NMR spectrum of oxolin is based on the difference in multiplicity observed for the signals from $C_{5(8)}$ and $C_{6(7)}$ measured without proton decoupling (Fig. 4*b*). The signal from $C_{5(8)}$ represents a doublet ($^1J_{CH}$ = 164.5 Hz) of multiplets (splitting due to the interaction with strongly coupled 6-H and 7-H protons). The signal from $C_{6(7)}$ is a doublet ($^1J_{CH}$ = 164.5 Hz) of doublets (splitting at the expense of $^3J_{metha}$ = 7.9 Hz for a weak interaction between 5-H and 8-H protons). This assignment agrees with the results of the chemical shift calculation for the oxolin benzene ring carbons. The calculation was performed using increments of the $COCH_3$ substituent in the benzene ring determined for carbon atoms occupying the *o*, *m*, and *p* positions with respect to the substituent [2].

The proposed assignment of signals from the benzene ring protons in the ^{1}H NMR spectrum of oxolin follows from the above assignment of signals due to the $C_{5(8)}$ and $C_{6(7)}$ carbons in the ^{13}C NMR spectrum and the 2D ^{13}C–^{1}H heterocorrelation spectrum (Fig. 5) in which the cross-peaks correspond to a direct (via single bond) spin – spin coupling between ^{13}C nucleus and proton.

EXPERIMENTAL BIOLOGICAL PART

The results of our experimental investigation showed that oxolin possesses a broad spectrum of antiviral action with respect to both RNA and DNA genome viruses [3].

TABLE 1. Virucidal Activity of Oxolin with Respect to APR-8 (H1N1) Influenza Virus

Oxolin concentration, μg/ml	Survival ratio* for virus dose		
	$1LD_{100}$	$10LD_{100}$	$100LD_{100}$
1000	20/20	20/20	0/20
100	20/20	20/20	0/20
10	20/20	0/20	0/20
Virus control	0/20	0/20	0/20

* Numerator and denominator indicate the number of mice that survived against the total number of animals tested.

TABLE 2. Oxolin Induced Inhibition of the Reproduction of A/41/57 (H1N1) Influenza Virus in Human Embryo Lung Diploid Cell Culture

Virus dose,* EID_{50}/cell	Oxolin concentration, μg/ml					
	HAR** titer in culture medium			Virus titer (EID_{50}) for chicken embryo infection		
	0	10	7.5	0	10	7.5
0.4	128	32	64	5.7	2.7	3.7
0.04	32	0	2	5.7	2.2	2.7
0.004	2	0	0	2.7	0	1.7

* EID_{50} – embryonal infection dose.
** HAR – hemagglutination reaction.

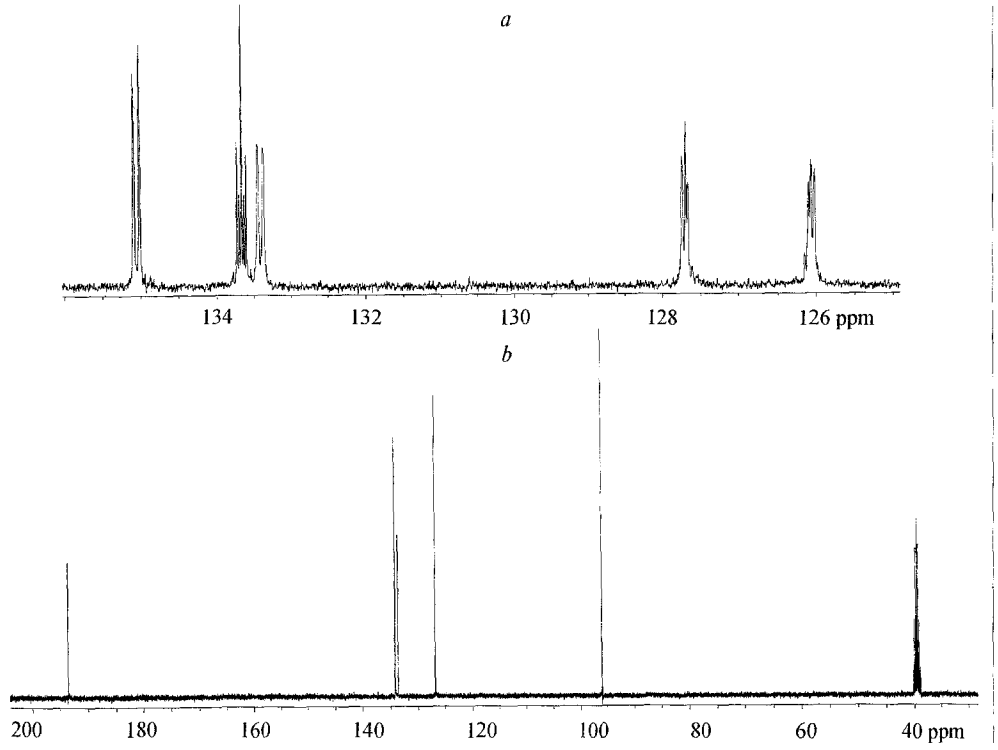


Fig. 4. ^{13}C NMR spectra of oxolin showing (*a*) the region of signals from benzene ring carbons measured without proton decoupling and (*b*) the total proton-decoupled spectrum.

During a 1-h contact *in vitro* at 14°C with a suspension of the lung tissue of white mice inoculated with the APR-8 (H1N1) influenza virus, oxolin at a concentration of 10 and 100 μg/ml fully suppressed the infection activity of the virus at an amount of one and ten LD_{50}, respectively (Table 1) [4]. Similar results were obtained for the virucidal properties of oxolin with respect to influenza viruses of a different antigen formula A/Aichi (H3N2), where the drug at a concentration of 10 μg/ml fully inhibited the infection activity of the virus taken in a dose of one LD_{100}. However, oxolin not only exhibited a virucidal effect in direct contact with the virus-containing material, but produced a virus-inhibiting action with respect to virus reproduction in the sensitive cells as well. For example, 10 and 7.5 μg/ml oxolin concentrations suppressed the growth of the A/41/57 (H1N1) influenza virus upon inoculation of a human embryo lung diploid cell culture by markedly (2.0 – 3.0 log ID_{50}) reducing the infectious titer and the hemagglutination activity of viruses against the control sample representing a monolayer of cells not treated with oxolin (Table 2).

The joint experiments performed with the Ivanovskii Institute of Virology (Moscow) showed that oxolin in a concentration of 75 and 50 μg/ml retarded development of the cytopathic effect, completely suppressed the hemagglutination activity, and markedly (3.2 – 3.7 logID_{50}) reduced the infectious titers of the A/FPV/Waybridge microvirus growing in a cell culture of chicken fibroblasts upon inoculation on a level of 0.1 BOD units per cell. At a lower viral infection multiplicity (0.001 – 0.01 BOD/cell), the viral growth was virtually completely inhibited by oxolin [5].

The inhibiting effect of oxolin upon the reproduction of influenza virus in sensitive sells was confirmed by *in ovo* experiments with ten-day chicken embryos inoculated in allantois vessels. The oxolin preparation in a dose of 0.5 and 1 mg per embryo inhibited reproduction of the A/PR-8/34(H1N1) virus in the embryos inoculated with 100 embryonal infection doses (EID_{50}). The infectious titers of this virus in groups of embryos treated with oxolin were lower by 4.0 – 5.0 log EID_{50} compared to the control level. The hemagglutination activity of the virus was also suppressed (Table 3).

To summarize the results of experimental investigation of the oxolin activity with respect to influenza viruses, it should be emphasized that this compound not only produces a virucidal action in direct contact with the intact virion, but reduces the level of virus reproduction in sensitive cells as well, suppressing the infection and hemagglutination activity of vi-

TABLE 3. Oxolin Induced Inhibition of the *in ovo* Reproduction of A/PR-8/34 (H1N1) Influenza Virus in Chicken Embryos Inoculated with 100 EID_{50}

Oxolin dose, mg/embryo	HAR titer (inverse values)		Virus titer (EID_{50})	
	Test	Control	Test	Control
0.5	194	3200	2.0	6.0
1	28	3200	1.0	6.0

* Each test group included nine chicken embryos.

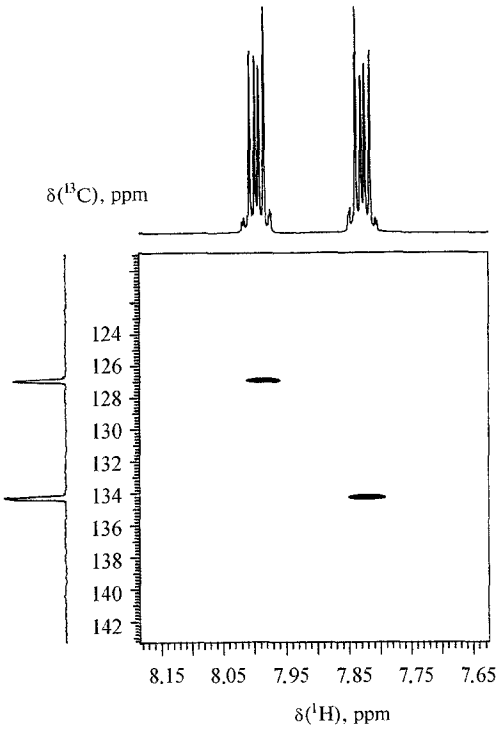


Fig. 5. Two-dimensional ^{13}C–^{1}H NMR heterocorrelation spectrum of oxolin in the region of signals from benzene ring carbons.

ruses. Apparently, this complex activity of oxolin is the basis for its antiviral effect with respect to influenza.

Investigations of the effect of oxolin upon some other RNA genome viruses showed that 50 – 90 μg/ml concentrations inhibit reproduction of the Venezuela encephalomyelitis virus in chicken fibroblast cell culture and offers protection to experimental mice inoculated with one or ten LD_{50} doses of West-American hoarse encephalomyelitis virus [6]. The oxolin dose of 250 μg per chicken embryo reduced by 40% the loss of embryos inoculated with the Newcastle disease virus against a 100% loss in the control [7].

The results of experimental and clinical investigations on DNA genome viruses showed that oxolin exhibits activity with respect to species such as herpes simplex virus, herpes zoster virus, Aujeszky's disease virus, adenoviruses, infectious verruca and molluscum contagiosum [8 – 12].

In addition to the pronounced antiviral activity, oxolin at a concentration of 250 – 1000 μg/ml produces *in vitro* a bacteriostatic action with respect to mycobacteria and a fungistatic effect on pathogenic fungi, in particular, dermatophytes.

Toxicological investigations showed that oxolin exhibits rather low general toxicity, with the LD_{50} value for white mongrel rats exceeding 700 mg/kg. In experiments on rabbits, oxolin produced no local irritation or resorption toxicity effects when applied in the form of a 5% ointment onto intact and scarified skin areas, introduced into a conjunctival eye sac, or instilled as a 10% aqueous solution into a nasal mucous membrane (all treatments performed once per day over a period of ten days). Oxolin induced no pathomorphological changes in the internal organs of experimental animals (gastrointestinal tract, pancreas, liver, kidney, heart, thymus, spleen, adrenal gland) and produced no detrimental changes in the peripheral blood (hemoglobin, erythrocytes, leukocytes, leukocytar formula) [13].

It was established that oxolin produces no teratogenic and embryotoxic effects and exhibits no immunodepressant activity [14].

After application of a ^{14}C labeled 2% oxolin ointment onto skin, about 5% of the compound was found in parenchymatous organs, this quantity increasing up to 20% after application of a 0.25% ointment onto the mucous membrane of the eye. Oxolin did not accumulate in the organism of experimental animals and was eliminated, predominantly with urine, within the first day after administration [15].

RESULTS OF CLINICAL INVESTIGATION

The main direction of the administration of oxolin in the form of an 0.25% ointment in medical practice is related to prophylaxis and treatment of influenza and other acute respiratory viral infections. A broad clinical investigation of this remedy was undertaken at the end of the 1960s and in the beginning of the 1970s by five leading medical centers of the USSR and involved a total of about 13.5 thousand patients.

For the purpose of individual prophylaxis of the influenza infection, 0.25% oxolin ointment was administered for daily application (once or twice per day) onto nasal mucous membrane over a seasonal epidemic period or during the period of contact with influenza patients.

The staff of the Central Sanitary-Epidemiological Station (USSR Ministry of Public Health, Moscow) studied the prophylactic efficacy of 0.25% oxolin ointment during the epidemic of 1969 in two cities. The experiment involved 9600 children under school age in 80 nursery schools. It was established that application of the ointment prevented infection in 43% of cases and made the course of the disease less severe in other cases. The frequency of complications in the form of pneumonia, bronchitis, and angina in the groups of children who received 0.25% oxolin ointment was 1.2 – 1.6 times lower compared to the control level. On the whole, the investigation showed a decrease in the level of infection in children treated with the 0.25% oxolin ointment, whereas the curve of infection kept increasing in the control groups [16, 17].

According to the data gained by the Lvov Research Institute of Epidemiology and Microbiology (Lvov, Ukraine), the prophylactic application of 0.25% oxolin ointment in a group of 611 scholars and students aged 15 – 18 reduced by 50% the level of infection with influenza and other acute respiratory diseases in patients who apply the ointment twice per day, and by 45% in patients treated once per day, that is, even a single daily application is sufficiently effective.

According to materials of the investigation performed by the Kishinev Sanitary-Epidemiological Station (Kishinev, Moldova), where the 025% oxolin ointment was administered to a total of 2939 people, the level of influenza infection in the test group decreased by 40 – 45%.

The effect of 0.25% oxolin ointment was also studied at the All-Union Research Institute of Influenza (USSR Ministry of Public Health, Moscow) on a model of experimental vaccinal influenza infection in a group of 176 volunteers. The results of this test also confirmed the prophylactic efficacy of the ointment. The absence of vaccinal influenza infection symptoms was observed in 45% of the test group, while the other patients exhibited a less severe course of the disease as compared to that in the control groups. Volunteers receiving the 025% oxolin ointment in a prophylactic mode showed a decrease in intensity of the immunological response to the introduction of living influenza vaccine.

The effect of 0.25% oxolin ointment was also studied in a group of 165 adult patients admitted to a hospital of the Clinical Department of the Ivanovskii Institute of Virology (USSR Ministry of Public Health, Moscow) with a diagnosis of medium-critical influenza. The ointment was applied to nasal passages 3 – 4 times per day, in addition to gargling fauces with a 0.25% oxolin solution prepared *ex tempore*. The treatment was continued for 4 – 5 days. The efficacy of this treatment was evaluated by monitoring the duration of the main clinical influenza manifestations (fever, intoxication, catarrhal symptoms) in the patients treated with oxolin in comparison to those in the control group. It was established that the local application of oxolin did not affect the duration of the period of fever and intoxication but reduced the period of catarrhal symptoms, decreases exudation, and improves nasal breathing. The Clinical Department recommended the 0.25% oxolin ointment for local application during the treatment of catarrhal symptoms in influenza patients [18 – 20].

To summarize the results of clinical investigation of the 0.25% oxolin ointment as a means of prophylaxis and therapy for influenza and other acute respiratory viral infections, we note that application of this ointment for the purpose of individual prophylaxis over epidemic periods prevents infection with influenza and other acute respiratory viral diseases in 45 – 50% cases, makes the course of disease less severe in infected patients, and reduces the risk of post-influenza complications. The ointment can also be used for rapid treatment of catarrhal symptoms in influenza patients. The oxolin ointment is well tolerated by both adults and children and has no side effects. Some patients may feel a slight nasal tingling sensation, which passes away rapidly.

The 0.25% oxolin ointment was recommended by the USSR Ministry of Public Heath as a remedy for the prophylaxis of influenza and for the treatment of influenzal rhinitis and has been successfully used since then (i.e., over almost three decades) during influenza epidemics.

The broad spectrum of antiviral activity inherent in oxolin, in particular, a pronounced virucidal action with respect to herpes simplex virus, was proved in experimental investigations performed using both cell cultures and *in vivo* models [4, 8, 9]. Following this, the therapeutic activity of the oxolin ointment of various concentrations was studied in patients suffering from herpetic disorders of the mucous membranes and skin.

Specialists at the Chair of Children Stomatology of the Institute of Medical Qualification Improvement (Moscow) investigated the effects of 0.25% oxolin ointment used for the therapy of 100 patients suffering from light and medium forms of acute herpetic stomatitis. The ointment was applied onto the affected parts for several minutes 3 – 4 times per day. It was established that 0.25% oxolin ointment prevented repeated eruptions of the damage, thus making less severe the course of the disease and shortening the time required for complete recovery. In particular, the duration of catarrhal gingivitis deceased by half. The ointment was well tolerated by children and was recommended for wide practical use in the treatment of acute heretic stomatitis in children [21, 22].

The Central Research Institute of Stomatology (Moscow) studied the therapeutic affects of 0.1% oxolin ointment and 0.05% aqueous solution in 150 patients suffering from various forms of stomatitis (acute herpetic, acute aphthous, recurrent chronic aphthous, and recurrent scarring stomatitis). The ointment was used applied to the affected parts, with a 3 – 5 min treatment repeated 4 – 6 times per day. The oxolin solution was used as a mouth gargle in cases of multiple damage of the mucous membrane in the oral cavity, which was also performed 4 – 6 times per day. It was found that oxolin treatments in most cases produced a positive effect even after only 1 – 2 days, as manifested by reduced tenderness of the affected area, decreasing surface erosion, and cleaning of the aphthae from fibrinous deposit and ulcers from necrotic mass. The time required for epithelization of the herpetic elements and aphthae decreases 3 – 4 times as compared to that in the absence of oxolin treatment. The best results were obtained when the treatment was begun within the first few days of infection [23].

It was also established that oxolin in the form of ointments is an effective remedy for the treatment of skin diseases induced by herpes simplex and herpes zoster viruses, but the concentration of the parent compound must be increased [10, 24].

The therapeutic properties of oxolin were also studied in four eye hospitals in different cities of the USSR. The investigation involved 247 patients, of which 124 had a diagnosis of herpetic keratitis and 123, of adenoviral keratoconjunctivitis [25 – 28]. In this test, oxolin was used in the form of a 0.2% solution and 0.25% eye ointment. Promising results were obtained in patients with both ophthalmic herpes and adenoviral eye infection. However, oxolin did not find wide application in ophthalmologic practice – on the one hand because special ophthalmic forms were not implemented into commercially produced and, on the other hand, because new and more effective remedies were developed for the treatment of viral eye diseases.

CONCLUSION

The results of experimental and clinical investigations showed that oxolin is an effective antiviral compound. The 0.25% oxolin ointment is successfully used for the individual prophylaxis of influenza and other acute respiratory viral diseases, as well as for the treatment of viral rhinitis. The 0.25% oxolin ointment has proved to be well tolerated by both adults and children, with no side effects. This is an advantage of the oxolin preparations over other drugs intended for systemic application. The 0.25% oxolin ointment is especially effective with respect to herpes viruses, which is very important if we take into account that influenza and other acute respiratory viral infections frequently lead to recidivating chronic latent herpetic infection with herpes labialis, herpes nasalis, and other clinical forms.

Of special attention is the possibility of using 0.25% oxolin ointment for the treatment of viral stomatitis. Treatment of skin disorders induced by herpes simplex and herpes zoster viruses requires application of elevated concentrations of oxolin.

REFERENCES

1. M. D. Mashkovskii, *Drugs* [in Russian], Torsing, Kharkov (1997), Vol. 2, p. 355.
2. G. Levy and G. Nelson, *Carbon-13 Nuclear Magnetic Resonance for Organic Chemists*, Academic Press, New York (1972).
3. G. N. Pershin, M. Ya. Kraft, N. S. Bogdanova, et al., *Khim.-Farm. Zh*, **4**(11), 56 – 58 (1970),
4. G. N. Pershin and N. S. Bogdanova, *Chemotherapy of viral Infections* [in Russian], Meditsina, Moscow (1973), pp. 40 – 42.
5. N. L. Pushkarskaya, N. A. Leont'eva, S. V. Grigor'ev, in: *Problems in Medical Virology. General Virusology* [in Russian], Meditsina, Moscow (1971), Vol. 11, pp. 242 – 244.
6. R. F. Gamidov and S. Ya. Gaidamovich, *Proc. Joint Session "Molecular Biology of Viruses, Chemotherapy and Chemoprophylaxis of Viral Infections* [in Russian], Minsk (1974), pp. 209 – 212.
7. N. I. Mitin, N. A. Lagutkin, F. A. Badaev, et al., *Proc. Joint Sess. "Molecular Biology of Viruses, Chemotherapy and Chemoprophylaxis of Viral Infections* [in Russian], Minsk (1974), pp. 230 – 235.
8. I. S. Nikolaeva, N. S. Bogdanova, G. N. Pershin, and S. N. Kutchak, *Farmakol. Toksikol.*, No. 3, 346 – 348 (1977).
9. Yu. F. Maichuk, *Viral Eye Diseases* [in Russian], Meditsina, Moscow (1981), pp. 50 – 51.
10. Yu. K. Skripkin, A. V. Khamaganova, and N. S. Bogdanova, *Vestn. Dermatol. Venerol.*, No. 9, 11 – 14 (1976).
11. F. V. Potapnev, A. A. Skuratova, O. I. Nyunikova, and G. A. Zhmurina, *Vestn. Dermatol. Venerol.*, No. 4, 68 – 70 (1975).
12. J. Gich and A. Denys, *Acta Microbiol. Pol.*, A-B, No. 3 – 4, 240 (1973).
13. *Oxolin*, Information Sheet No. P409 / 580, Vneshtorgizdat Moscow (1971).
14. L. N. Filitis and G. N. Pershin, *New Chemotherapeutic Preparations for the Therapy of Patients Suffering from Infection Diseases. A Collection of Scientific Papers of the All-Union Inst. Pharm. Chem.* [in Russian], Moscow (1976), Vol. 5, pp. 193 – 206.
15. V. A. Ovchinnikova, P. P. Filatov, and V. A. Chernov, *Khim.-Farm. Zh*, **11**(9), 24 – 27 (1977),
16. V. A. Aksenov, D. A. Selidovkin, G. N. Gladkikh, et al., *Farmakol. Toksikol.*, No. 6, 726 – 733 (1970).
17. V. A. Aksenov, D. A. Selidovkin, G. N. Gladkikh, et al., *Pediatriya*, No. 4, 18 – 22 (1970).
18. A. A. Alekseeva, G. N. Pershin, N. S. Bogdanova, and M. Ya. Kraft, *Influenza and Acute Respiratory Diseases* [in Russian], Meditsina, Leningrad (1967), pp. 90 – 92.
19. D. M. Zlydnikov, Yu. A. Romanov, and V. I. Romanovskii, *Farmakol. Toksikol.*, No. 5, 590 – 593 (1970).
20. G. I. Karpukhin and S. S. Glitarov, *Modern Remedies and Methods of Influenza Prophylaxis* [in Russian], Meditsina, Leningrad (1977), pp. 125 – 128.
21. L. N. Drobot'ko, T. A. Stul'neva, and N. I. Bronshtein, *Current Problems in Child Stomatology* [in Russian], Meditsina, Moscow (1974), pp. 43 – 45.
22. T. V. Vinogradova, L. N. Drobot'ko, N. I. Bronshtein, et al., *Stomatologiya*, No. 5, 61 – 63 (1974).
23. M. I. Lyalina, *Antiviral Preparations Created at the All-Union Inst. Pharm. Chem.* [in Russian], Min. Med. Prom., Moscow (1972), Part 1, pp. 33 – 35.
24. P. T. Biletchenko, L. P. Korolev, and N. S. Bogdanov, *Antiviral Preparations Created at the All-Union Inst. Pharm. Chem.* [in Russian], Min. Med. Prom., Moscow (1972), Part 1, pp. 35 – 39.
25. E. E. Kuhar', *Proc. 10th Sci.-Pract. Conf. Ophthalmologists* [in Russian], Moscow (1965), pp. 152 – 154.
26. N. N. Kaminskaya, *Current Problems in Clinical Medicine* [in Russian], Izd. Krasn. Gos. Univ., Krasnoyarsk (1966), pp. 420 – 421.
27. A. A. Verzin and G. P. Belikov, *Antibiotics and Chemotherapeutic Preparations and Their Practical Application* [in Russian], Izd. Akad. Nauk UkrSSR, kiev (1970), pp. 51 – 52.
28. Yu. F. Msichuk and O. V. Rzhechitskaya, *Antiviral Preparations Created at the All-Union Inst. Pharm. Chem.* [in Russian], Min. Med. Prom., Moscow (1972), Part 1, pp. 18 – 20.