

The evaluation of humoral response and the clinical evaluation of a risk-group patients' state of health after administration of the homeopathic preparation Gripp-Heel during the influenza epidemic season 1993/94

L.B. Brydak¹, A. Denys²

¹National Influenza Center WHO, Dept. of Virology, National Institute of Hygiene, Warsaw, Poland

²Department of Microbiology, University School of Medicine, Łódź, Poland

SUMMARY

The evaluation of humoral response and the clinical evaluation of a risk-group patients' state of health after administration of the homeopathic preparation Gripp-Heel during the influenza epidemic season 1993/94

L.B. Brydak¹, A. Denys²

¹National Influenza Center WHO, Dept. of Virology, National Institute of Hygiene, Warsaw, Poland

²Department of Microbiology, University School of Medicine, Łódź, Poland

Int. Rev. Allergol. Clin. Immunol., 1999; Vol. 5, No. 4

In the autumn of 1993 eighty three volunteers – chronically ill residents of nursing homes received Gripp-Heel preparation (ampoules and tablets). The patients' clinical state was systematically observed during 6 months of the epidemic season 1993/94. Antibody production was determined in sera samples collected before treatment with Gripp-Heel and three and four weeks after drug administration using the hemagglutinin inhibition (HI) test and neuraminidase inhibition (NI) test. Three weeks after the administration of Gripp-Heel geometric mean antibody titers (GMTs) for hemagglutinins H1, H3 and HB were about 2 times higher than before treatment. In the control group GMTs were nearly on the same level and the infections with the influenza virus registered in this group. Three weeks after drug administration GMT for neuraminidase N1 was 9.5 times higher than before drug administration, while for neuraminidase N2 it was 15.4 times higher and for neuraminidase NB it was 8.0 times higher. The highest value for neuraminidase was observed for antigen A/Beijing/32/92.

The clinical data we obtained indicate seroprotection against influenza after the administration of Gripp-Heel when compared with the control group.

Key words: influenza; humoral response

STRESZCZENIE

Ocena odpowiedzi humoralnej i stanu klinicznego chorych z grup ryzyka po podaniu preparatu homeopatycznego Gripp-Heel w czasie epidemicznych zachorowań na grypę w sezonie 1993/94

L.A. Brydak¹, A. Denys²

¹Narodowy Ośrodek WHO ds. Grypy, Zakład Wirusologii, Instytut Higieny, Warszawa, Polska

²Zakład Mikrobiologii Wojskowej Akademii Medycznej, Łódź, Polska

Int. Rev. Allergol. Clin. Immunol., 1999; Vol. 5, No. 4

Jesienią 1993 r. 83 ochotników – przewlekle chorych pensjonariuszy domu opieki – otrzymało preparat Gripp-Heel (ampułki i tabletki). Stan kliniczny chorych był systematycznie obserwowany w ciągu 6 miesięcy sezonu zachorowań 1993/94. Określano wytwarzanie przeciwciał w próbkach surowicy zebranych przed leczeniem Gripp-Heel oraz trzy i cztery tygodnie po podaniu leku, używając testów zahamowania hemaglutynacji i neuraminidazy. Trzy tygodnie po podaniu Gripp-Heel średnie geometryczne miano przeciwciał dla hemaglutyniny H1, H3 i HB były blisko 2 razy wyższe niż przed leczeniem. W grupie kontrolnej średnie wartości były niemal na tym samym poziomie oraz odnotowano zakażenie wirusem grypy. Trzy tygodnie po podaniu leku średnie geometryczne miano przeciwciał dla neuraminidazy N1 było 9,5 razy wyższe niż przed leczeniem, podczas gdy dla neuraminidazy N2 aż 15,4 razy wyższe, a dla neuraminidazy NB – 8,0 razy wyższe. Najwyższe wartości miana przeciwciał dla neuraminidazy stwierdzono dla antygenu A/Beijing/32/92.

Uzyskane dane kliniczne wskazują na seroprotekcję przeciwko grypie po podaniu Gripp-Heel w porównaniu do grupy kontrolnej.

Słowa kluczowe: grypa; odpowiedź immunologiczna

Each year influenza and its complications account for 10 000-40 000 excess deaths in the United States. Over 80% of those deaths occur among the elderly. Furthermore, during some epidemics of influenza A there have been approximately 172 000 extra hospitalizations due to influenza and pneumonia. The cost of severe influenza epidemic has been almost 12 billion dollars (8, 10).

Influenza appears mostly in the epidemic and sometimes even pandemic form. It causes high incidence of the disease and consecutively increase of mortality. The most common reasons of death are complications such as pneumonia during epidemic or just afterwards (6, 9) and aggravation of chronic respiratory and cardiovascular diseases. In spite of the fact that all age groups are susceptible to flu, complications are most common among children and adults over 65. In order to limit the number of death cases and to reduce social costs of flu (massive absence) there are preventive vaccinations carried out in many countries in the period preceding the flu season (4).

The protective action is carried out in the risk groups (senile people with chronic respiratory and cardiovascular diseases, people staying in concentration e.g. residents of nursing homes, boarding-schools, orphanages). The society's and physicians' attitude towards active prevention of flu (vaccination) is still distrustful in spite of many enlightening actions. This situation causes that the medical world look for other methods of prevention against influenza infections. Basic direction of management consists in the administration of preparations that enhance the organism's immunity. There are many hopes concerning immunostimulative vegetal extracts and homeopathic drugs (5).

The aim of the present paper is the assessment of humoral response and clinical evaluation in elderly people with chronic medical condition after the administration of the homeopathic preparation Gripp-Heel.

MATERIAL AND METHODS

Patients: The subjects were 124 chronically ill residents of nursing homes. The most common chronic diseases (according to the case records) were generalised artheromatosis, cerebral artherosclerosis, coronary artheromatosis, myocardiopathy of artherosclerotic origin, senile dementia, senile psychosis and diabetes.

Inmates were randomly divided into two groups. There were 73 (av. 68.2 years of age) subjects in the study group and 51 in the control group. The youngest was 53 years old and the oldest was 96 (mean age 71.5). During the whole study all patients were under medical care.

Antibody production was determined in sera before drug administration and then three and also four weeks after receiving the Gripp-Heel preparation by the hemagglutinin inhibition (HI) test and neuraminidase inhibition (NI) test. The same procedures were carried out in the control group. The collected sera were stored at -20°C until tests were made.

Drug: Gripp-Heel is a composed homeopathic preparation produced by the German firm Heel. It consists of both vegetable (*Aconitum*, *Bryonia*, *Lachesis*, *Eupatorium perfoliatum*) and mineral (Phosphorus) components. All components are in low concentrations (D2, D11) and they fulfil all Homeopathic Pharmacopoeia requirements. The Gripp-Heel preparation is produced in the form of p.o. tablets and ampoules (1.1 ml solution in the suspension of 0.9% NaCl solution) for s.c., i.c., i.m. and in exceptional cases i.v. injections. The patients from the study group were given 1 amp. of the Gripp-Heel preparation i.m. (in the brachial muscle). The treatment was continued by giving tablets for suction - 3 times a day for 14 days. The control group was administered 1.1 ml of 0.9% NaCl solution and placebo tablets in the same manner. The following parameters were evaluated: local and general reactions (1 and 3 days after infusion). The patients' clinical state was systematically observed during 6 months of the epidemic season (taking incidence of diseases and death into account).

Serological tests: Hemagglutinin inhibition (HI) tests were performed by a routine technique. Neuraminidase activity and neuraminidase inhibition (NI) tests were performed according to Aymard-Henry's method with fetuin used as a substrate (1).

Prior to reaction, sera had been inactivated in a water bath at 56°C for 30 min. Serological results were measured by HI and NI tests carried out with A/Texas/36/91 (H1N1), A/Beijing/32/92 (H3N2) and B/Panama/45/90 antigens in collected samples of sera. The antigens mentioned above were prepared in our laboratory, i.e. WHO National Influenza Center, Dept. of Virology, National Institute of Hygiene, Warsaw.

Serological parameters: The following parameters were used to express the humoral immune response to hemagglutinin and neuraminidase:

1. The geometric mean of antihemagglutinin or anti-neuraminidase antibodies before drug administration and after three and four weeks.
2. The mean fold increase of antihemagglutinin or antineuraminidase antibody titers after drug administration.

For humoral immune response to hemagglutinin, additional parameters were used:

1. Protection rate, i.e. the proportion of subjects showing HAI antibody titer $\geq 1:40$ before and after drug administration.

2. Response rate, i.e. the proportion of subjects showing at least a fourfold titer increase after drug administration.

Results obtained in the study group and in the control group were statistically analyzed by using the ANOVA test.

RESULTS

There were no local or general adverse events after injection in both groups. There were no side reactions after the administration of Gripp-Heel in tablets. During 6 months of observation, there were 4 cases of falling into sickness in the Gripp-Heel and 11 in the control group. There were 2 cases of acute bronchitis, 1 case of spastic bronchitis, 1 case of chronic bronchitis aggravation and 1 case of dental abscess in the control group. During the observation period there were 5 death cases in the study group and 9 in the placebo group. All of them were classified to be of natural causes.

The geometric mean titers (GMTs) in Table 1 and Table 2 illustrate the level of HI and NI antibody changes before the administration of Gripp-Heel and three weeks after treatment in a group of elderly people with chronic medical conditions as compared with the control group. Three weeks after administration of the homeopathic preparation Gripp-Heel the mean fold increase (MFI) ranged from 1.9 to 2.1, while in the control group it was a little lower for hemagglutinin H1 (1.6) and hemagglutinin H3 (1.4), but slightly higher for hemagglutinin HB (2.2) because of the influenza infections clinically observed in the control group. The proportion of subjects showing HI antibody titers $\geq 1:40$ was very low in the case of H1, but for H3 and HB it ranged from 66% to 97%. All parameters used to express the humoral immune response to hemagglutinin clearly indicated that for antigen A/Beijing/32/92 (H3N2) higher values were found

Table 2. Antibody response to neuraminidase components of influenza viruses (H1N1, H3N2 and HB) in elderly people suffering from chronic diseases after administration of homeopathic preparation Gripp-Heel in 1993 in Poland

Antigen	Group	Geometric mean antibody titer		Mean fold increase
		before	after	
		drug administration		
A/Texas/36/91 (H1N1)	A	6.1	57.8	9.5
	B	6.4	11.5	1.8
A/Beijing/32/92 (H3N2)	A	5.6	86.3	15.4
	B	5.8	11.0	1.9
B/Panama/45/90	A	4.7	37.6	8.0
	B	4.9	9.8	2.0

A – group receiving drug (n=73)

B – control group (n=51)

when compared with the control group. On the other hand results obtained in this study showed that people in the control group were infected with type B of influenza virus which was antigenically similar to strain B/Panama/45/90.

In the case of another component, namely neuraminidase, three weeks after drug administration GMT for neuraminidase N1 amounted to 57.8, for N2 – 86.3 and for NB – 37.6. Mean fold increase values were 9.5, 15.4 and 8.0, respectively. In the control group MFI indexes ranged from 1.8 to 2.0.

Antibody response to hemagglutinin and neuraminidase of the influenza virus in elderly people suffering from chronic diseases after the administration of Gripp-Heel (Fig. 1) clearly emphasized much better response to neuraminidase glycoprotein than to hemagglutinin. Differences of the humoral response levels observed between the study group and the control group were statistically significant ($p < 0.05$). The homeopathic preparation Gripp-Heel used in this study was well tolerated both in the injected form and in tablets.

Table 1. Antibody response to hemagglutinin components of influenza viruses (H1N1, H3N2 and HB) in elderly people suffering from chronic diseases after administration of homeopathic preparation Gripp-Heel in 1993 in Poland

Antigen	Group	Geometric mean antibody titer		Mean fold increase	Proportion of subjects protected (%)		Response rate (%)
		before	after		before	after	
		drug administration			drug administration		
A/Texas/36/91 (H1N1)	A	2.1	4.0	1.9	0/73 (0)	2/73 (3)	2/73 (3)
	B	2.1	3.4	1.6	0/51 (0)	0/51 (0)	0/51 (0)
A/Beijing/32/92 (H3N2)	A	20.5	40.7	1.9	35/73 (48)	48/73 (66)	11/73 (15)
	B	12.8	18.4	1.4	7/51 (14)	13/51 (25)	1/51 (2)
B/Panama/45/90	A	60.2	126.2	2.1	60/73 (82)	71/73 (97)	18/73 (25)
	B	82.2	178.4	2.2	45/51 (88)	51/51 (100)	12/51 (23)

A – group receiving drug (n=73)

B – control group (n=51)

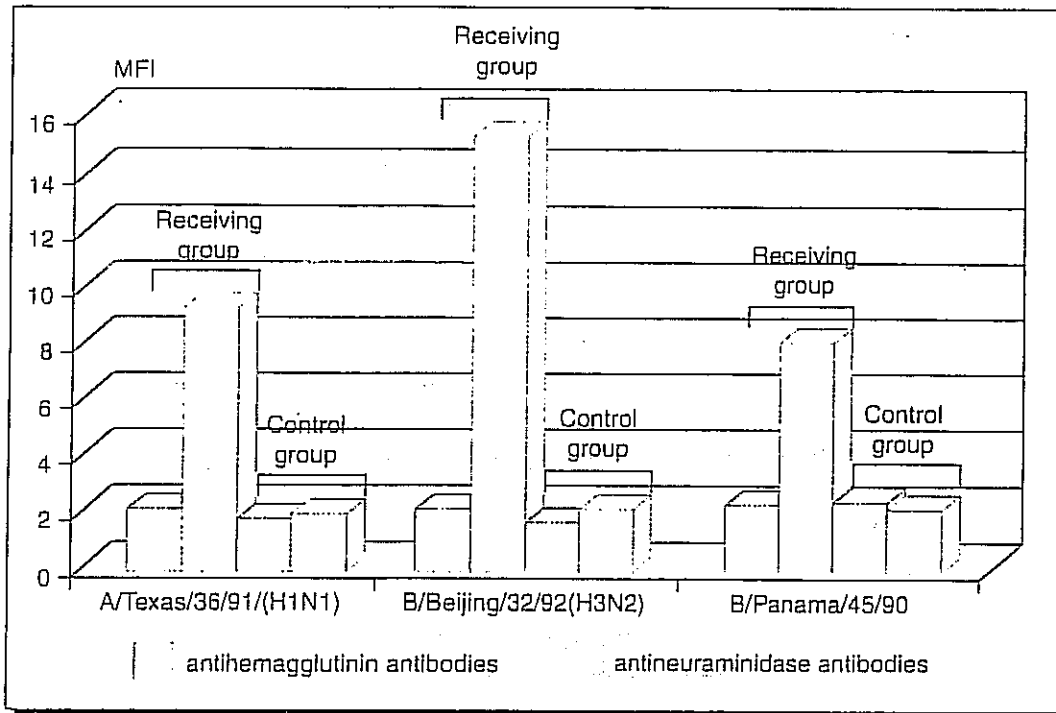


Fig. 1. Mean fold increase (MFI) for anti-hemagglutinin and anti-neuraminidase antibodies in elderly people suffering from chronic diseases after administration of homeopathic preparation Gripp-Heel in the epidemic season 1993/94 in Poland.

DISCUSSION

Elderly persons and persons with underlying health problems are at increased risk for complications of influenza. For this reason influenza vaccine is strongly recommended for patients such as these. Therefore in many parts of the world national and international health authorities recommend annual vaccine administration for subjects being at risk for influenza associated complications (4, 6).

According to WHO and ACIP recommendations elderly people with chronic medical conditions should be protected against influenza infections. There is no doubt that vaccination of these patients is one of the best ways of prevention. This is a problem for all organizations working in health service (2).

The main contraindication for influenza vaccine is anaphylactic hypersensitivity to eggs or to other vaccine components. On the other hand there are some groups of patients which do not want to be vaccinated without any reason. A person who has a contraindication for influenza vaccination may be a candidate for amantadine, rimantadine or for other antiviral drugs used for prophylaxis, especially in high-risk patients – chronically ill residents of nursing homes. However, currently available antiinfluenza drugs, i.e. amantadine and rimantadine cannot be used commonly for a few reasons. One of them is that these compounds face rapid appearance of drug resistant mutants.

Flu spreads very quickly endangering people's health in all age groups. It is the most dangerous for patients of high-risk groups (6, 10). There has been no analysis of economic losses caused by influenza

made in Poland. However, according to the Institute of the Medicine of Labour in Łódź, respiratory tract diseases are the most common reasons of absence (these data are presented in Table 3) (2, 9). Gripp-Heel is a preparation that has been used for a long time in the treatment of viral infections, so-called influenza-like infections. Numerous tests proved the effects of its action – 20% – 40% increase of phagocytosis activity (5, 11). Human volunteers and mice studies showed its efficacy in the protection against respiratory viruses (7, 12, 13). Due to the low toxicity of this preparation it can be an alternative for persons who do not receive vaccine for different reasons. Our studies indicate that offering Gripp-Heel to patients helps in prevention against influenza infections, but this is more evident in the case of neuraminidase. Similar results were obtained in elderly people with chronic medical conditions after vaccination against influenza carried out in Poland in the same epidemic season 1993/94 (3).

In effect, antibodies against the viral NA do not prevent the infection, but they significantly reduce viral replication and hence the occurrence and severity of the illness (2, 4). There is no doubt that during an epidemic of influenza elderly people with chronic medical conditions living in nursing homes should be protected against influenza infections. It is generally accepted that the immunological system works less effectively in elderly people, although this opinion is not shared by everyone. A lot of scientific research workers try to prepare a drug which would be effective against all strains of influenza viruses and which would give a long lasting protection.

Table 3. Number of employed people on sick leave in Poland in 1985-1993 (data obtained from bulletins from the Institute of the Labour Medicine in Łódź)

Year	Number of reported influenza cases	Number of sick leave days due to		Number of sick leaves per 100 of employed people (sick leave index)		Diseases of respiratory tract
		influenza	pneumonia, bronchitis and bronchiolitis	influenza	pneumonia, bronchitis and bronchiolitis	cause of sick leave
1985	2 309 875	4 535 865	6 048 795	38.20	50.90	26.7%
1986	1 578 975	4 705 170	6 968 556	39.10	57.80	26.9%
1987	1 218 292	4 812 295	6 831 238	39.50	56.10	26.6%
1988	628 690	2 362 921	6 085 195	20.01	51.54	24.0%
1989	1 642 126	4 588 511	6 544 765	39.21	55.93	26.4%
1990	80 161	1 579 809	4 853 036	13.89	42.66	20.5%
1991	1 968 468	3 299 398	5 122 587	32.68	50.74	21.5%
1992	256 692	1 598 405	4 401 070	18.24	50.23	19.7%
1993	2 706 911	4 365 906	5 025 311	52.65	60.60	21.8%

CONCLUSIONS

The homeopathic preparation Gripp-Heel is well tolerated in an injectable form and in tablets as well. It did not cause any severe adverse reactions. Protective administration of this drug decreases disease incidence – especially of respiratory tract diseases, reducing the risk of chronic sickness aggravation and death. Due to the above mentioned features the Gripp-Heel preparation should be considered a valuable protective agent against acute viral infections of the upper respiratory tract (including influenza) in persons from risk groups, especially in cases in which no protective vaccine can be administered.

Gripp-Heel antiviral drugs can be administered prophylactically to anyone who wishes to avoid an influenza illness after considering the risk and benefits in consultation with their healthcare provider.

Acknowledgements

The authors are grateful to Dr Ewa Ordyńska and Dr Bogdan Wasilewski for assistance.

REFERENCES

1. Aymard-Henry M., Coleman M.T., Dowdle W.R., Laver W.G., Schild G.C., Webster R.G.: *Influenza virus neuraminidase and neuraminidase-inhibition test procedures*. Bull. WHO, 1973, 48, 199.
2. Brydak L.B.: *Influenza prophylaxis*. Przegl. Epidemiol., 1996, 50, 31-38 (in Polish).
3. Brydak L.B., Ordyńska E., Wasilewski B., Rudnicka H., Regnery H., Cox N.: *Immunogenicity of trivalent subunit influenza vaccine in elderly people with chronic medical conditions vaccinated in 1993 in Poland*. Antimicrob. Drugs and Chemotherapy, 1997, 15, 1, 9-12.
4. Cox N.J., Bender C.A.: *The molecular epidemiology of influenza viruses*. Seminars in Virology, 1995, 6, 359-370.
5. Denys A.: *Practical application of natural immunostimulators in the treatment of chronic infections*. Med. Biol., 1995, 3/4, 67-76 (in Polish).
6. Ghendon Y.: *Influenza surveillance*. Bull. WHO, 1991, 69, 509-515.
7. Kleijnen J., Knipschild P., Riet G.: *Clinical trials of homeopathy*. BMJ, 1991, 302, 316-323.
8. Knottnerus J.A.: *Influenza in the Netherlands*. PharmacoEconomics, 1996, 9, 46-49.
9. Magdzik W., Brydak L.B.: *Influenza: problem in Poland as elsewhere*. Arch. Immunol. Ther. Exp., 1996, 35, 201-206.
10. Palache A.M.: *European scientific Working Group on Influenza (ESWI)*. PharmacoEconomics, 1996, 9, 1-3.
11. Wagner H.: *Examination of the immune-stimulation effect of some plant homeopathic drugs*. Biol. Ther., 1997, IV (2), 21-27.
12. Werner T.: *Gripp-Heel experimentally investigated, proven in practice*. Biological Therapy, 1987, IV (1), 13-14.
13. Werner T.: *The effective principle of Gripp-Heel*. Biol. Ther., 1997, IV (3/4), 47-52.

Correspondence: L.B. Brydak, National Influenza Center WHO, Dept. of Virology, National Institute of Hygiene, Chocimska Str. 24, Warsaw, Poland