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Search of new myelostimulators among piperidine compounds

Studied the group of of chemical compounds, bi-and monocyclic piperidine derivatives in complexes with β-cyclodextrin under laboratory code BIV. The highest results were found to stimulate leucopoies compound BIV-69. Compounds BIV-68 and BIV-71 stimulated lymphopoiesis. Myelopoiesis stimulated compounds BIV-69 and BIV-71.
Keywords: bi- and monocyclic piperidine derivatives, leucopoies, lymphopoies, myelopoies.

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Пиперидин туындылардың арасында жаңа миелостимулдаушы перапатарды іздеу

БИВ лабораторлық шифрмен анықтылатын β-циклодекстрин комплекс түрінде би- және моноциклдық пиперидин қосылыстары зерттелген. Нәтижесінде ең жақсы лейкопоэзді стимулдайтың қосылыс БИВ-69 көрсетті. Қосылыстар БИВ-68 және БИВ-71 лимфопоэзды стимулдады. Ал миелопоэзді БИВ-69 және БИВ-71 қосылыстары белсендетті.
Түйін сөздер: миелостимулятор, би- және моноциклдық пиперидин қосылыс, лейкопоэз, лимфопоэз, миелопоэз.

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Поиск новых миелостимуляторов среди производных пиперидина

Исследована группа соединений, би- и моноциклических производных пиперидина в виде комплексов с β-циклодекстрином под лабораторным шифром БИВ. Наиболее высокие результаты по стимулированию лейкопоэза показало соединение БИВ-69. Соединения БИВ-68 и БИВ-71 активно стимулировали лимфопоэз. Миелопоэз стимулировало соединения БИВ-69 и БИВ-71.
Ключевые слова: миелостимулятор, би- и моноциклический производный пиперидина, лейкопоэз, лимфопоэз, миелопоэз.

Currently in medical clinical practice drugs using with myelosuppressive effects. But of effective drugs, capable myelostimulated in a short time myelogram in the peripheral blood and bone marrow, is very limited. Furthermore, myelostimulators are widely used in ophthalmology, surgery, cosmetics and biotechnology. Thus, pharmacological screening of drugs on the mielostimulate activity relevant today.

Materials and Methods

We used healthy adult animals – laboratory rats of both sexes, the age 10-15 weeks, body weight 210-280 g and during the experiment in the control and experimental animals were kept under the standard conditions, on the standard diet, per cage for 6 animals. Blood sampling was performed from the orbital vein of rats anesthetized with ether anesthesia weak at 09.00 am. A blood test was performed on a hematology analyzer for laboratory animals «Abacus junior vet» (made in Denmark, Diatron). Myelosuppressiv effectse induced by intramuscular administration of cytostatic cyclophosphamide sodium of 30 mg/kg animal body weight. Experimental groups of animals were administered compound at a dose of 10 mg/ml (solvent saline) intramuscularly at a volume of 0.5 mL daily for 3 days, 3 days after the last administration was determined number of

cells in the peripheral blood. Control animals of the same amount and mode saline. The comparator was pantogematogen.

Results and Discussion

Control values obtained from intact animals admitted to the experiment were within the physiological range. Leukocyte index (9,1 ± 2,51) $\cdot 10^9$/L blood with lymphocyte (5,46 ± 1,1) $\cdot 10^9$/L blood that was (60,9 ± 0,9)%. Granulocytic leucocytes were significant (3,64 ± 0,9) $\cdot 10^9$/L blood to the percentage in leucogram (40,0 ± 0,4)%. Minimum rate was monocyte (05,0 ± 0,0) $\cdot 10^9$/L blood that was leucogram (6,0 ± 0,7)%. As indicators of erythrocytes and platelets were normal. Erythrocyte figure was (6,5 ± 1,4) -10^{12}/L blood hemoglobin content (140,7 ± 1,2) g / L , respectively, and blood hematocrit (39,8 ± 1,9)%. Only platelet was slightly reduced (350,6 ± 3,6) $\cdot 10^9$/L of blood , as well as thrombocrit was only (12,6 ± 0,3)%. But in general, the main parameters of blood received by the experiment animals were normal. Directed immunosuppressive effect of cyclophosphamide administered sodium led to myelodepressive syndrome with falling blood indicators already the first day after administration. Leukocyte common figure was (4,15 ± 1,2) $\cdot 10^9$/L blood, from 2.19 times reduction ($p \leq 0,05$) and on the third day after the administration was leukocyte (2,69 ± 0,54) $\cdot 10^9$/L of blood that was 3.40 -fold drop in relative to control ($p \leq 0,01$). By leucogramm blood can note significant negative changes of cell pools of lymphocytes, granulocytes, monocytes. Indicators of immune cells – lymphocytes with the reference value (5,46 ± 1,1) -10^9/L of blood fell on the first day before (2,46 ± 0,75) $\cdot 10^9$/L blood and reached on the third day are (1,99 ± 0,18) $\cdot 10^9$/L of blood , 2.74 -fold ($p \leq 0,05$). Even more significant changes occurred in cell populations of granulocytes. Level of granulocytic leukocytes from the value (3,64 ± 0,9) -10^9/L blood fell to the 1st day before (1,33 ± 0,18) -10^9/L blood , 5.28 times ($p \leq 0,01$). The percentage of such a sharp decline has not been fixed. Reduction of granulocytes was on the third day after the administration of cyclophosphamide (23,75 ± 8,55)%, 1.68 times. A significant reduction in the absolute granulocyte indicator 5.28 times compared with a moderate decrease in the relative rate of granulocytic leukocytes 1.68 times may explain the significant drop in the total leukocyte index, which affected the absolute values of cells in the blood.

Some increase in monocytes was observed on the first day after the administration of cyclophosphamide, which can be explained by the massive loss of cells and an increase in functional load. Indicator intact animals (6,0 ± 0,7)% by the 1st day after cyclophosphamide became (7,05 ± 4,6)%, but on the third day after he fell to the introduction of (0,6 ± 0.0) % , 10 times from the control values ($p \leq 0,01$).

In red blood cells, such as significant changes in leukocyte cell populations were observed. Some fluctuations erytrocyte cells from (6,5 ± 1,4) -10^{12}/L of blood with a decrease of the first day before (4,71 ± 1,37) $\cdot 10^{12}$/L, 1.38 times and a slight increase up to (5,80 ± 0,27) $\cdot 10^{12}$/L on the third day after the administration cyclophosphamide. Also a trend in the fluctuations of indicators on the first day and third day after cyclophosphamide sodium observed in the values of hemoglobin, hematocrit, mean corpuscular volume, mean content of hemoglobin in erythrocyte cells, the breadth of the distribution of red blood cells . Declines were observed on the first day of 1.2-1.6 times with a further increase in value. Significant changes were recorded in terms of platelets, which naturally affected the values trombocryts, mean platelet volume and platelet distribution breadth. Already on the first day after administration of cyclophosphamide sodium platelet count fell to (345,0 ± 126,0) $\cdot 10^9$/L of blood during the control value (500,0 ± 147,0) $\cdot 10^9$/L blood , i.e 1.45 ($p \leq 0,05$). By the third day after the administration of the platelet count fell to (74,5 ± 39,5) $\cdot 10^9$/L of blood from the control value (500,0 ± 147,0) $\cdot 10^9$/L blood, 6.71 -fold ($p \leq 0,01$). This figure is considered critical and is characterized by spontaneous bleeding and other intracavitary hemophilitical disorders.

Thus, we can conclude that cyclophosphamide caused myelosuppression and most sensitive cells were leukocyte cells and platelets. Among leukocyte cells died primarily lymphocytes, granulocytes, monocytes and more. Further background on myelodepressive syndrome of the animals were administered azogeterocycle compound under the code “BIV”. Among all the compounds showed high activity compounds BIV -68, and BIV -69, BIV -70, scourged BIV -71. They stimulate the proliferation activity of bone marrow cell pools, and stimulated emission lymphomyeloid cells

from peripheral organs. Among these compounds, the compound showed high activity BIV-69. In the group of animals with the introduction of the compound BIV-69 already on the 6th day after the first administration of the compound absolute leukocyte index was (6,51 ± 0,4) $\cdot 10^9$/L blood, against a reference value (2,79 ± 0,92) $\cdot 10^9$/L blood, which was 2.33 – fold difference ($p \leq 0,05$). In terms of absolute cell indicators to lead compound BIV -69. In this group of animals lymphocytic figure was (3,53 ± 0,12) $\cdot 10^9$/L blood against the reference value (1,55 ± 0,88) $\cdot 10^9$/L blood , in excess of 2.28 times ($p \leq 0,05$). Level of monocytes in absolute value was (0,32 ± 0,2) $\cdot 10^9$/L blood against the reference value (0,12 ± 0,1) $\cdot 10^9$/L blood. Best values were also against granulocytic leukocytes, accounting (2,65 ± 0,06) $\cdot 10^9$/L blood against the reference value (1,13 ± 0,14)-10^9/L, exceeding 2.35 times ($p \leq 0$, 05). However, the relative values of BIV-69 , despite the higher absolute values were lower than in the administration of the compound BIV -68. The maximum value of lymphocytes was in the group administering the compound BIV -68 accounting (68,0 ± 0,8)%, exceeding the relative values of lymphocytes in groups administering compounds BIV -71 (65,0 ± 3,3)%, BIV -70 with a value of (56,9 ± 0,4)% and scourged BIV -69 with a value of (54,3 ± 1,8)% and with the control value (50,65 ± 14,65)%. But as seen from the values of especially significant differences were observed in the readings, so pay attention to the absolute values of lymphocytes with emphasis on compound BIV -69. The rest of the relative performance of granulocytic leukocytes, monocytes directly correlated with absolute values. The maximum values of the absolute indicator of granulocytic leukocytes active compound BIV-69 was (2,65 ± 0,06) $\cdot 10^9$/L blood against the reference value (1,13 ± 0,14) $\cdot 10^9$/L of blood , exceeding 2.35 times ($p \leq 0,05$). Correlating absolute value with a relative refractive index expressed in blood granulocytes (40,8 ± 0,9)% against the reference value (33,35 ± 9,35)% and against the values of Group administration of the compounds BIV -69 (29,5 ± 3 , 1 %) and compound BIV -71 (29,97 ± 1,04)%. The values of monocytes in the group administering the compound BIV -69 was the maximum value in research groups and was (0,32 ± 0,2) $\cdot 10^9$/L blood connection BIV -70 (0,02 ± 0,0) $\cdot 10^9$/L blood connection BIV -70 (0,16 ± 0,1) $\cdot 10^9$/L blood against the reference value (0,12 ± 0,1) $\cdot 10^9$/L blood. The relative importance of monocytes was also the highest in animals with administration of the compound BIV -69 , making (4,9 ± 2,8)% against the values in the administration of the compound groups BIV -68 , BIV -70, BIV -71 and scourged the following : (2,4 ± 1,2)%, (0,7 ± 0,0)% and (4,03 ± 3,31)% , respectively (Table 1).

Table 1 – Indicators hemogramms of the peripheral blood

Group	common leukocyte indicator (WBC, $\cdot 10^9$ /L)	Abs. count granulocyte ($\cdot 10^9$/L) rel. count granulocyte (%)	Abs. count lymphocyte ($\cdot 10^9$/L) rel. count lymphocyte (%)	Abs. count monocytes ($\cdot 10^9$/L) rel. count monocytes (%)	Criteria of validation
intact	9,1±2,51	3,64±0,9 40,0±1,4	5,46±1,1 60,0±0,7	0,5±0,0 6,0±0,4	
control	2,785±0,92	1,125±0,135 43,35±9,35	1,545±0,875 50,65±14,65	0,115±0,095 6,0±5,3	p_{2-1}<0,01- 29,00%
BIV-68	3,0±0,06	0,88±0,04 29,5±3,1	2,04±0,06 68,0±0,8	0,07±0,04 2,4±1,2	p_{3-2}<0,01- 83,6%
BIV-69	6,51±0,0	2,65±0,06 40,8±0,9	3,53±0,12 54,3±1,8	0,32±0,2 4,9±2,8	p_{4-2}<0,05- 37,6%
BIV-70	3,52±0,02	1,49±0,02 42,4±0,36	1,67±0,33 56,9±0,4	0,02±0,0 0,7±0,00	p_{5-2}<0,05- 56,5%
BIV-71	3,28±0,03	0,98±0,04 29,97±1,0	2,13±0,13 65,0±3,3	0,16±0,1 5,03±3,31	p_{6-2}<0,05- 37,2%
Immuno depressiv syndrom	2,675±0,535	0,685±0,355 23,75±8,55	1,985±0,175 75,65±8,55	0,015±0,005 0,6±0,0	

BIV-69 connections also stimulated proliferative activity of red blood cells: erythrocytes and platelets. The erytrocyte indicator for the 6th day after primary introduction of connection of BIV-69 made blood (6,52±0,0) $\cdot 10^{12}$/L, exceeding control value (5,67±2,58) $\cdot 10^{12}$/L of blood and indicators in groups of introduction of connections of BIV-68, BIV-70, BIV-71, making (3,24±0,03) $\cdot 10^{12}$/L of blood, (4,43±0,02) $\cdot 10^{12}$/L of blood and blood (4,9±0,06) -10^{12}/L respectively. All values connection of BIV-68, BIV-70, BIV-71 conceded in groups of introduction to BIV-69 value in 2,01; 1,47; 1,33 times respectively. The content of hemoglobin in group of introduction of BIV-69 made 110±0,5 g/L blood that exceeded value in groups of introduction of connections of BIV-68, BIV-70, BIV-71 in 1,87; 1,35 and 1,21 times respectively, making (58,7±0,4) g / L; (81,6±0,5) g/L and (91,0±0,7) g/ L of blood. The similar picture was observed and on other erytrocyte indicators: hematocrite, to the average volume of erythrocytes, average concentration of hemoglobin in erytrocyte and a distribution range of erythrocytes. Leading indicators were fixed in group of animals with introduction of connection of BIV-69, conceded to BIV-70, further there was BIV-71 and the last place was taken by BIV-68.

Concerning platelets it is possible to make the conclusion that connection of BIV-69 stimulated also division of platelets. Level of platelets reached by 6th day of supervision of value (509,0±1,0) $\cdot 10^{9}$/L of blood against control value (44,0±0,5) $\cdot 10^{9}$/L of blood and against in groups of introduction of connections of BIV-68, BIV-70, BIV-71 of the following values (232,3±3,77) $\cdot 10^{9}$/L of blood (342,0±6,7) $\cdot 10^{9}$/L of blood respectively.

It is undoubted that connections of BIV-69 is leading concerning myelostimulate properties.

Refferences

1 Diamonds V.A., Afanasiev B.V., Zaritsky A., Shishkov A.L. Leukopenias. – L.: Medical, 1981. – 240 p.

2 Kinetic aspects of hematopoiesis / Ed. G.I. Kozinets, E.D. Goldberg. – Tomsk, 1982. – 311.

3 Hershanowitch M.L. Complications of chemotherapy and hormonal therapy of malignant tumors // Malignant. neoplasms. – M., 1982. – 223 p.

4 Adams J. A., Barrett A. J. Haematopoietic stimulators in the serum of patients with severe aplastic anaemia // Brit. J. Haemat. – 1982. – vol. 52, N 2. – p. 327 – 335.

5 Anderson M. J. The emerging story of a human parvovirus-like agent // J. Hyg. Camp. – 1982. – vol. 89, N.2. – p. 1- 10.

6 Dessypris E. N., McKee G. L., Metzontonakis C. Ptire red cell aplasia associated with chronic granulocytic leukemia // Brit. J Haemat. -1981. – vol 48, N 2. – p. 217 – 225.

7 Ding Xun-Jie, Li Yuan, Ding Yur. Chromosome changes in patients with chronic beuzeae poisoning // Chinese med. J. – 1983. – vol. 96, N 9. – p. 681- 685.

8 Ershler W. B., Ross J., Finlay L., Shahidi N. T. Bone Marrow microenvironment defect in congenital hypoplastic anemia // New Engl J. Med. – 1980. – vol. 302. – p. 1321 – 1327.

9 Kanamaru A., Hara H., Nagai K. Hemopoietic stem cells and their regulatory factors in aplastic anemia // Acta Haemat. Jap. – 1981. – vol 44, N.7. – p. 1332 – 1340.

10 Khelif A., Vuvan H., Tremisi J. P. et al. Remission of acquired pure red cell aplasia following plasma exchanges // Scand. J. Haemat. – 1985, N 34. – p. 13 – 15.

11 O′Brien H., Amess J. A., Mollin D. L. Reccurent thrombocytopenia, erythroid hypoplasia and sideroblastic anaemia associated with hypothermia // Brit. J. Haemat. – 1982, vol. 51. – p. 451 – 456.

12 Otsuca Y., Nino Y., Goto I. A case of aplastic anemia following viral hepatitis B // J. Kyu Hem. Soc. – 1984. – vol. 32, N 1 – 2. – p. 38 – 41.