Notes

Hydroxyurea. A New Type of Potential Antitumor Agent[1]

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Previous investigations in our laboratories with derivatives of hydroxylamine, including the cyclic hydroxamic acids, led to a number of potent antibacterial and antifungal agents.[2] To continue our study of the structure–activity relationships in this series we had prepared hydroxyurea[3] and related compounds. In spite of the previous reports that hydroxyurea was ineffective in RC mouse mammary carcinoma[4] and Sarcoma 180,[5] we have investigated hydroxyurea in leukemia, since it had been reported to alter leukocyte formation by bone marrow in experimental animals.[6]

Screening results now have shown that hydroxyurea itself is effective against the standard L 1210 leukemia in mice upon intraperitoneal or oral administration and typical dose responses are given in Table I. In addition, preliminary tests indicate that upon intraperitoneal administration hydroxyurea is active against a variety of other leukemias, being effective against L 1210 strains resistant to amethopterin, 2-amino-6-purinethiol or 8-azaguanine. On the other hand, it shows only slight activity against L 5178Y-A leukemia and marginal activity against a 5-fluorouracil-resistant leukemia P 815/Fu-A. In the preliminary screening it has not shown activity against L 1210 leukemia resistant to 6-mercaptopurine. These results are summarized in Table II. It is also of interest that hydroxyurea is active against the solid tumor, LB 82T leukemia, since at a dose of 100 mg./kg. it causes a 91% inhibition of tumor growth in mice.

TABLE I

ANTILEUKEMIC ACTION OF HYDROXYUREA *vs.* L 1210[a]

Dose in mg./kg.	Average wt. change of mice[c]	Average life span	% Increase in life span[d]
	INTRAPERITONEAL[b]		
25	+0.3	10.7	32
50	−0.5	13.0	60
100	−1.3	14 3	76
200	−1.1	12.3	51
400	−1.0	16.2	100
Controls	+2.2	8.1	—
	ORAL		
175	−1.2	12.8	39
250	−0.9	14.4	56
400	−1.0	16.4	78
600	−1.8	15.7	70
Controls	+1.4	9.2	—

[a] Groups of 10 mice were given 1,000,000 leukemic cells by intraperitoneal injection 24 hr. prior to initiation of therapy. [b] Groups of 10 mice were treated by intraperitoneal injection once a day for the duration of life or 15 days (whichever is shorter). [c] Animals weighed on 7th day after leukemic inoculation. [d] An increase in life span of 25% over control animal is significant.

TABLE II

ANTILEUKEMIC ACTION OF HYDROXYUREA AT 100 MG./KG.[b]

See Table I for explanation of footnotes

Strain[a]	Average wt. change of mice[c] Treated	Average wt. change of mice[c] Controls	Average life span Treated	Average life span Controls	% Increase[d] in life span
L 1210	0	+1.3	13.9	8.9	56
L 1210/8-AG-A	−0.2	+2.1	18.9	13.2	43
L 1210/Ameth-A	+0.6	+2.2	16.6	9.7	71
L 1210/6-MP-A	−0.5	+2.2	25.7	21.9	17
L 1210/6-TG-A	0	+2.7	29.1	15.7	85
L 5178Y-A	+1.6	+3.8	17.0	12.3	38
L P815/Fu-A	+0.8	+2.0	16.5	13.4	23

In view of these results with hydroxyurea itself, a number of analogs and derivatives have been prepared. Alkyl derivatives were synthesized by the reaction of a hydroxylamine with potassium cyanate (A) or an alkyl isocyanate (B).[7] Acyl derivatives were prepared by treatment of hydroxyurea with an acylating agent (C)[8] or by the reaction of an acyl isocyanate with a hydroxylamine (D).[9] A detailed description of these syntheses and the properties of the compounds prepared, as well as the results of the antitumor screening, will be published shortly.

$$\text{(A)}\quad \text{RNHOH} \xrightarrow{\text{HCNO}} \text{H}_2\text{NCONROH}$$

$$\text{(B)}\quad \text{R'NHOH} \xrightarrow{\text{RNCO}} \text{RNHCONR'OH}$$

$$\text{(C)}\quad \text{H}_2\text{NCONHOH} \xrightarrow{(\text{RCO})_2\text{O}} \text{H}_2\text{NCONHOCOR}$$

$$\text{(D)}\quad \text{R'CONCO} \xrightarrow{\text{RNHOH}} \text{R'CONHCONROH}$$

On the basis of the screening results hydroxyurea[10] has been selected for clinical evaluation in the treatment of leukemia.

(1) The biological data reported here were obtained at the screening laboratories of the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health.

(2) E. Shaw, J. Bernstein, K. Losee, and W. A. Lott, *J. Am. Chem. Soc.*, **72**, 4362 (1950).

(3) In this paper, the name hydroxyurea is used to denote the compound $NH_2CONHOH$, m.p. 145–146° dec. The so-called low melting isomer (m.p. 72°) of hydroxyurea has been shown to be O-carbamoylhydroxylamine: M. Davies and N. A. Spiers, *Spectrochim. Acta*, 487 (1959); H. Kofod, *Acta Chem. Scand.*, **13**, 461 (1959); see also O. Exner, ref. 8.

(4) G. S. Tarnowski and C. C. Stock, *Cancer Research*, **18**, No. 8, Part 2, Compound 6878.

(5) C. C. Stock, D. A. Clarke, F. S. Philips, R. K. Barclay, and S. A. Myron, *ibid.*, **20**, No. 5, Part 2, Compound 19968.

(6) F. Rosenthal, L. Wislicki and L. Koller, *Klin. Wochschr.*, **7**, 972 (1928).

(7) L. Francesconi and A. Parrozzani, *Gazz. Chim. Ital.*, **31**, II, 343 (1901).

(8) O. Exner, *Collection Czech. Chem. Commun.*, **22**, 335 (1957).

(9) W. A. Lott, J. Bernstein and B. Stearns, U. S. Patent 2,999,110 (1961); *Chem. Abstr*, **56**, 7213 (1962).

(10) Hydrea®.