INVESTIGATION OF THE ACTION OF SIX ALKALOIDS DERIVED FROM 1-METHYLPYRROLIZIDINE ON THE GROWTH OF HEPATOMA AND OTHER TRANSPLANTED ANIMAL TUMORS

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Compounds with a well-marked characteristic action on certain tissues of the body are of undoubted interest for investigation of their possible action also on tumors arising from these tissues.

Plant alkaloids of the genus Senecio, Heliotropium and certain others are derivatives of 1-methylpyrrolizidine, and are complex esters, splitting up on saponification into aminoglycols (heliotridin, retronecin, platynecin, etc.) or amino alcohols (for example trachelantemidine) and acids (heliotrinic, lasiocarpinic, senecioninic, viridiflorinic, etc.). The alkaloids of this group are known to possess marked hepatotoxic properties [10-12] and, in addition, some of these alkaloids, when introduced into the body over a long enough period of time, cause the development of tumors in the liver of animals [13-15]. According to some findings, chronic alkaloid poisoning is associated with changes in the metabolism of the liver cell, leading to an increase in the concentration of copper in the liver. This is shown pathohistologically mainly by an increase in the size of the liver cells and their nuclei, and by a decrease in the regenerating power of the liver tissue, although in isolated cases foci of hyperphasia may also be observed [10, 11, 13].

We investigated the action on a hepatoma transplanted subcutaneously into mice of line C_3HA of six alkaloids, the chemical structure and properties of which have been described in the literature (heliotrine [4], viridiflorine [6-8], platyphilline [3, 9], seneciphilline [3, 9], lasiocarpine [4, 5] and heliosupine [2]). The strain of transplantable hepatoma which we used was obtained and described by V. I. Gel'shtein [1]. At the same time, we investigated the action of these same alkaloids on the growth of an Ehrlich's tumor, grafted subcutaneously and in some cases, on the growth of sarcoma 45 of rats.

EXPERIMENTAL METHOD AND RESULTS

The drugs were injected intraperitoneally once a day. Heliotrine was used in its basic form, platyphillin as the bitartrate, and the remaining 4 alkaloids as the hydrochloride.

As shown by the results of an investigation of the toxicity, given in the table, the most toxic were seneciphillin, lasiocarpine and heliosupine, whereas the other three alkaloids were less toxic. From a comparison

Results of an Investigation of the Toxicity and the Inhibitory Action on the Growth of Tumors of the Alkaloids Investigated

Experiment No.	Preparation	100% lethal dose, mg/kg	Therapeutic dose, mg/kg	Tumor	Day after transplantation when expt. started	Duration of treatment, in days	Number of animals: experiment	Number of animals: control	Inhibition of tumor growth by comparison with controls in wt. %
1	Heliotrine	400 (for mice)	40	Hepatoma	8	14	10	10	8
2	»		100	Ehrlich's tumor	5	12	10	10	0
3	»	300 (for rats)	20	Sarcoma 45	7	14	15	15	0
4	Viridiflorine	500 (for mice)	100	Hepatoma	8	14	10	10	0
5	The same		100	Ehrlich's tumor	5	12	10	10	0
6	Platyphillin	400 (for mice)	100	Hepatoma	8	14	10	10	0
7	The same		120	Ehrlich's tumor	5	12	10	10	0
8	Seneciphillin	120 (for mice)	20	Hepatoma	8	14	10	10	10
9	The same		20	Ehrlich's tumor	5	12	10	10	19
10	Lasiocarpine	300 (for mice)	20	Hepatoma	9	14	10	10	21
11	»		30	Ehrlich's tumor	5	12	10	10	0
12	»	100 (for rats)	10	Sarcoma 45	7	14	15	15	17
13	Heliosupine	150 (for mice)	40	Hepatoma	8	14	14	14	0
14	»		50	Ehrlich's tumor	5	12	10	10	54
15	»	100 (for rats)	15	Sarcoma 45	7	14	10	10	28

of the values of the lethal dose (LD_{100}%) of heliotrine, lasiocarpine and heliosupine, determined in mice and rats it followed that rats were more sensitive to the toxic action of these compounds than mice. Approximately the same relationships held good for the therapeutic doses for rats and mice.

It was found that mice of the C_3 HA line with hepatoma were slightly more susceptible to the toxic action of these drugs when given repeatedly, than mongrel mice with Ehrlich's tumor.

When the alkaloids were given in the therapeutic doses shown in the table, none of the animals under observation died in the course of the 12-14 days of the experiment, but after its completion the majority of the mice showed dystrophic changes, as mentioned above, in the liver in agreement with the findings of other authors [10-13].

The only exception was viridiflorine, for after administration of this drug the liver was normal in appearance. In this connection it must be remembered that viridiflorin is a complex ester, not of an amino glycol, like the rest of the alkaloids under test, but of an amino-alcohol — trachelantamidine. This difference in its structure evidently accounts for the difference in its action on the liver. However,

notwithstanding the toxic action of nearly all the alkaloids investigated on the liver only one of them (lasiocarpine) had a slight inhibitory action on the growth of the hepatoma (see table).

Investigation of the action of the same compounds on the growth of the Ehrlich's tumor showed that only heliosupine give a significant inhibitory effect (54 % inhibition by comparison with the controls); repetition of the experiment gave the same result. Seneciphillin inhibited growth of this tumor only to a slight degree (19%), and the remaining compounds tested had no action on its growth. A weak inhibitory action on the growth of sarcoma 45 was shown by lasiocarpine and heliosupine.

As a result it can be stated that, although three of the compounds investigated — seneciphillin, lasiocarpine and heliosupine — possess slight antitumor activity, this does not agree, as we thought at first, with the toxicological organotropy of the compounds of this group, since they do not exhibit their main action on the hepatoma, even in the case of heliosupine, when the antitumor activity which is present is expressed as a considerable inhibition of the growth of Ehrlich's tumor.

The pronounced toxic action of these compounds on the normally functioning liver and their lack of action on malignant tissue give grounds for suggesting that in this case the toxic action of the drugs is connected with a function of the normal liver that is absent from tumor cells derived from the tissue of that organ. In such cases, toxicological organ-specificity naturally provides no clue in the search for antitumor preparations.

SUMMARY

Investigations were made to determine the toxicity and the effect of 6 alkaloids (heliotrine, viridiflorin, platyphillin, seneciphilline, lasiocarpine and heliosupine) on the growth of subcutaneously inoculated hepatoma of mice and Ehrlich's adenocarcinoma. The greatest inhibitory effect on the growth of the hepatoma was shown by lasiocarpine. A considerable inhibitory effect on Ehrlich's tumors was also exerted by heliosupine.

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