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THE METABOLISM OF CYCLOPHOSPHAMIDE-^{14}C BY VARIOUS MARINE SPECIES

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Cyclophosphamide (Cytoxan®) is an anticancer agent which is activated by an enzyme system in the liver microsomes of mammals. In mammals the production of the effective anticancer agent is inhibited by SKF-525-A and is increased threefold by pretreatment with phenobarbital.

Data presented in this abstract based on in vivo experiments demonstrates that the nurse shark (Ginglymostoma cirratum), the dogfish (Squalus acanthias), crayfish (Palinurus argus), and lobsters (Homarus americanus) can also metabolize Cytoxan.

The nurse shark metabolized Cytoxan to a greater extent than the dogfish and SKF-525-A appeared to inhibit this metabolism in the former species in vivo (Tables 1, 2 and 3). Both unchanged Cytoxan and metabolites were excreted into the bile of both elasmobranchii studied. Temperature difference alone does not account for the difference in Cytoxan metabolism between the warm water abiding nurse shark and the colder habitat of the dogfish (14-15° C), since both lobsters from Maine (Table 4) and crayfish from the Bahamas (Table 5) were able to metabolize the drug to an appreciable extent. Levels of metabolite in the hepatopancreas of the

Table 1

PLASMA AND LIVER LEVELS OF CYTOXAN-^{14}C AND METABOLITES IN MALE NURSE SHARKS FOLLOWING INTRA-ARTERIAL INJECTION OF 10 MG/KG

Shark number		Time in hours	Unchanged Cytoxan μg/ml or gm	Percent of ^{14}C	
				as unchanged Cytoxan	as metabolites
1	Plasma	1	20.4	75.0	25.0
		2	18.1	82.0	18.0
		4	15.4	77.7	22.3
		8	13.1	87.7	12.3
		12-1/2	12.9	93.8	6.2
		24	10.9	100.0	0
	Liver	24	13.7	88.4	11.6
2	Plasma	1	19.0	65.5	34.5
		2	16.6	67.7	32.2
		4	15.4	71.9	28.1
		8	12.3	83.8	16.2
		12-1/2	12.3	88.3	11.7
		24	10.0	99.2	0.8
	Liver	24	12.5	78.1	21.9

Table 2

PLASMA AND TISSUE LEVELS OF CYTOXAN-^{14}C AND METABOLITES IN MALE NURSE SHARKS PRETREATED WITH SKF-525-A (10 MG/KG, INTRA-ARTERIALLY) 30 MINUTES PRIOR TO I.A. INJECTION OF 10 MG/KG CYTOXAN-^{14}C

Shark number		Time in hours	Unchanged Cytoxan μg/ml or gm	Percent of ^{14}C	
				as unchanged Cytoxan	as metabolites
3	Plasma	1	13.8	91.2	8.8
		2	12.8	90.5	9.5
		4	11.4	90.5	9.5
		8	10.5	92.2	7.8
		12-1/2	10.3	91.9	8.1
		24	9.6	94.4	5.6
	Liver	24-1/2	9.2	81.1	18.9
	Bile	24-1/2	79.6	25.1	74.9
4	Plasma	1	19.7	94.5	6.5
		2	18.0	92.9	7.1
		4	16.0	92.4	7.6
		8	14.9	97.1	2.9
		12-1/2	14.3	96.9	3.1
		24	12.1	95.4	4.6
	Liver	24-1/2	14.1	91.3	8.7
	Bile	24-1/2	66.1	38.1	61.9

Table 3

PLASMA AND TISSUE LEVELS OF CYTOXAN-^{14}C AND METABOLITES IN DOGFISH FOLLOWING INTRA-ARTERIAL INJECTION OF 10 MG/KG

Dogfish number		Time in hours	Unchanged Cytoxan μg/ml or gm	Percent of ^{14}C	
				as unchanged Cytoxan	as metabolites
1	Plasma	1	14.7	92.7	7.3
		2	12.7	91.7	8.3
		4	11.8	93.2	6.8
		8	10.8	95.7	4.3
		19	9.4	95.7	4.3
		24	8.8	96.6	3.4
	Liver	24	6.8	93.2	6.8
	Bile	24	121.4	46.2	53.8
2	Plasma	1	16.1	95.7	4.3
		2	13.7	90.5	9.5
		4	12.9	95.3	4.7
		8	12.2	95.8	4.2
		19	10.8	96.2	3.8
		24	9.8	96.3	3.7
	Liver	24	8.0	94.4	5.6
	Bile	24	78.2	44.9	55.1

Table 4

BLOOD AND TISSUE LEVELS OF CYTOXAN-^{14}C AND METABOLITES IN THE LOBSTER FOLLOWING INTRAVENOUS ADMINISTRATION OF 30 MG/KG

Lobster number		Time in hours	Unchanged Cytoxan μg/ml or gm	Percent of ^{14}C	
				as unchanged Cytoxan	as metabolites
1	Blood	1	40.6	90.9	9.1
		24	10.4	63.4	36.6
	Hepatopancreas	24	10.8	37.3	62.7
2	Blood	1	42.3	89.9	10.1
		24	4.1	26.4	73.6
	Hepatopancreas	24	6.1	30.8	69.2
3	Blood	1	39.8	93.5	6.5
		24	5.4	55.6	44.4
	Hepatopancreas	24	6.7	30.8	69.2

Table 5

BLOOD LEVELS OF CYTOXAN-^{14}C AND METABOLITES IN CRAYFISH FOLLOWING INTRAVENOUS ADMINISTRATION OF 30 MG/KG

Time in hours	Unchanged Cytoxan μg/ml	Percent of ^{14}C	
		as unchanged Cytoxan	as metabolites
1*	27.9	65.9	34.0
3-1/2†	19.6	50.7	49.3
15‡	10.3	68.0	32.0

*Average of two groups, each consisting of pooled blood from 2 crayfish.

†Average of three groups, one consisting of pooled blood from 2 crayfish, the other consisting of blood from 2 separate crayfish.

‡Average of 5 crayfish.

lobster exceeded those for the parent compound. Other observations suggest that the hepatopancreas of the lobster can metabolize other foreign compounds (Brodie and Maickel, Proc. First Int. Pharmacol. Mtg. 6:299, 1962). Although the gills of the lobster are relatively more permeable than those of the dogfish to a substance as lipid soluble as antipyrine (Rall et al., Bull. Mt. Desert Island Biol. Lab. 6:31, 1966), the lobster apparently metabolizes the lipid soluble Cytoxan to a much greater extent than the dogfish.

Therefore, Cytoxan as well as other foreign compounds are capable of being metabolized by fish and other aquatic species by processes of reduction, oxidation, hydrolysis or conjugation (Fed. Proc. 26:1047, 1967).