LACK OF CARCINOGENICITY OF 8-NITROQUINOLINE ON LONG-TERM IN VIVO TEST IN HAMSTERS

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Abstract.....Syrian golden hamsters were administered 8-nitroquinoline, at a concentration of 0.05%, in a 10% ethanol solution as drinking water for 104 weeks. The animals were kept under observation until 112 weeks of age when the experiment was terminated. Both control and treated groups developed tumors in a pattern indistinguishable from that usually observed in Syrian golden hamsters. Thus the result of this experiment indicates that 8-nitroquinoline given orally at a concentration of 0.05% is not carcinogenic in Syrian golden hamsters.

Key words: 8-nitroquinoline; carcinogenicity test; hamster; spontaneous tumor

INTRODUCTION

The carcinogenic effect of quinoline derivatives has been studied by Nakahara and his colleagues (Nakahara et al., 1957) and other investigators (Endo et al., 1971; Kawachi et al., 1976; Kawazoe et al., 1967; Lacassagne et al., 1966; Takayama, 1962.)

In particular, the carcinogenicity of 4-nitroquinoline 1-oxide and related compounds has attracted attention with tumor induction being demonstrated in rats, mice, guinea pigs, hamsters and rabbits (Endo et al., 1971; Mori, 1967; Mori, 1965; Takahashi, et al., 1969). Furthermore, 4-nitroquinoline 1-oxide and related compounds have also been shown to induce papillomas of the skin by topical application (Endo et al., 1971; Takayama, 1962).

On the other hand, Hirao et al. have reported that quinoline itself is carcinogenic (Hirao et al., 1976).

8-Nitroquinoline has been shown to be mutagenic using *salmonella typhimurium* tester strains TA100 and TA98 with, but not without, S-9 mix (Nagao et al., 1977) and in a previous paper (Takahashi et al., 1978) reported that oral administration of 8-nitroquinoline to Sprague-Dawley rats leads to the induction of tumors in the pharynx, esophagus, forestomach and lung. Fukushima et al. also reported that 8-nitroquinoline was carcinogenic to F344 rats (Fukushima et al., 1981).

In contrast, the results of the present long term *in vivo* assay of carcinogenicity of 8-nitroquinoline in Syrian golden hamsters indicate a lack of activity with no evidence for either tumor induction or potentiation of spontaneously occurring neoplasms.

MATERIALS AND METHODS

One hundred randomly bred, 8-week-old Syrian golden hamsters of both sexes purchased from the Japan Laboratory Animals Inc., Tokyo, were housed in screen-bottomed cages in groups of 4. Animals were fed a commercial pelleted diet (Oriental MF, Oriental Yeast Co., Tokyo, Japan) *ad libitum* maintained under standard conditions (room temperature: $23 \pm 2^\circ\text{C}$, humidity: $55 \pm 5\%$) and weighed weekly. 8-Nitroquinoline (98.0% purity) was purchased from Nakarai Pure Chemical Co., Ltd., Kyoto, Japan and was administered at a concentration of 0.05%, the compound first being dissolved in 98% ethanol and then diluted to 10% (v/v) in tap water, because 0.05% 8-nitroquinoline was maximum dose limited by the problem of solubility. Control groups were given 10% (v/v) ethanol solution without 8-nitroquinoline until the end of the experiment. Hamsters were sacrificed under ether anesthesia after 112 weeks or when they became moribund.

Animals that died before 60 weeks were excluded from the effective numbers of animals, all others (the effective number) undergoing a complete autopsy with the tumors being examined macroscopically and microscopically. Tissues were fixed in 10% buffered-formalin, embedded in paraffin, sectioned and routinely stained with hematoxylin and eosin.

RESULTS

The lifetime body weight curves and survival rate curves of both 8-nitroquinoline-treated and control groups were comparable (Figs. 1, 2). Throughout the experimental period, there was no significant difference in general physical condition between experimental and control groups.

Table 1 shows the incidence of tumors in each group. Gross and histologic patterns of each tumor type were similar among the different groups. Statistical tests indicated no significant association of the treatment with tumor incidence.

Tumors occurred most frequently in the adrenal gland. Adrenal cortex adenomas were found in 4 males and 3 females in the control group and in 6 males and 2 females in 8-nitroquinoline groups. A & B cell tumors of cortical origin were more frequent in the male control group. Pheochromocytomas were observed in 3 hamsters of the female control group.

Fig. 1. Mean body weight of male and female hamsters treated with 8-NQ.

Fig. 2. Survival rate of male and female hamsters treated with 8-NQ.

Forestomach tumors occurred with very low frequency; microscopically, there were a total of 4 papillomas in the control groups and 1 squamous cell carcinoma in the 8-nitroquinoline groups. Tumors were also found in other organs in each group, although at very low incidences as shown in table 1.

DISCUSSION

Mutagenicity tests of 8-nitroquinoline were positive with *S. typhimurium* tester strains TA100 and TA98 in the presence of the S-9 mix system (Nagao et al., 1977) and thus it could be assumed that enzymatic activation is essential for carcinogenicity of 8-nitroquinoline. The results of an earlier studies clearly demonstrated that 8-nitroquinoline administered in a semisynthetic diet for 48 weeks is carcinogenic in Sprague-Dawley (Takahashi et al., 1978), primarily affecting the upper digestive tract and this result was confirmed with F344 rats (Fukushima et al., 1981). In contrast to the former experiment using rats, 8-nitroquinoline given in the drinking water did not show a significant increase in tumor incidence in Syrian golden hamsters.

Although the mechanisms underlying carcinogenesis and the reasons for the selective organotropic effect of this chemical are unknown, 8-nitroquinoline primarily induced tumors of the rat upper digestive tract, which is characterised by a squamous cell epithelium (Takahashi et al., 1978). 4-Nitroquinoline 1-oxide has a similar effect in rats (Takahashi et al., 1969) and mice (Mori, 1967), but 2-nitroquinoline does not (Mori et al., 1969). However, hamsters administered 8-nitroquinoline in the drinking water demonstrated only sporadic development of proliferative lesions in the forestomach.

8-Nitroquinoline, 4-nitroquinoline and 2-nitroquinoline also have been reported to

Table 1 Tumor incidence in hamsters treated with 8-nitroquinnoline.

Site and type of tumor or other lesion	Dose level(%) :	No. of hamsters with tumors			
		Males		Females	
		0	0.05	0	0.05
Effective No. of hamsters		20	16	22	25
HEMATOPOIETIC SYSTEM					
Multiple organs					
Leukemia		0	0	0	1
Spleen					
Hemangioendothelioma		1	0	0	0
ENDOCRINE SYSTEM					
Thyroid gland					
Hyperplasia		1	0	0	0
C-cell adenoma		0	0	0	1
Adrenal gland					
Cortical					
Hyperplasia		1	1	1	0
Adenoma		4	6	3	2
A&B cell tumor		3	0	0	0
Pheochromocytoma (bengin)		2	0	3	0
Pancreas					
Insular hyperplasia		1	0	0	0
Insuloma (bengin)		0	1	0	0
RESPIRATORY SYSTEM					
Trachea					
Hyperplasia		1	0	1	0
Papilloma		0	1	1	0
Lung Adenoma		0	1	0	0
Squamous cell carcinoma		0	1	0	0
DIGESTIVE SYSTEM					
Esophagus					
Hyperplasia		1	0	0	0
Forestomach					
Hyperplasia		0	3	0	0
Papilloma		3	0	1	0
Squamous cell carcinoma		0	0	0	1
Glandular stomach					
Hyperplasia		0	0	0	1
Liver					
Cholangioma		0	0	1	0
REPRODUCTIVE SYSTEM					
Uterus					
Endometrial hyperplasia				1	0
Adenocarcinoma				0	1
Myoma				0	1
INTEGUMENTARY SYSTEM					
Skin					
Papilloma		0	0	1	0
Malignant melanoma		1	0	0	0

induce lung adenomas (Mori et al., 1969; Mori et al., 1969; Takahashi et al., 1969). However, in this experiment only 1 adenoma and 1 squamous cell carcinoma were observed in the treated males but no tumors in the females. Therefore we concluded these tumors could be spontaneous in nature. In this study neither in the upper digestive tract nor in the lung were any clear correlations between development of lesions and 8-nitroquinoline treatment.

The discrepancy between the results of the present study and those of the previously published rat study indicates that species differences in carcinogenicity studies should be considered.

As another factor, we gave the chemical in the drinking water in this experiment while in the former experiment administration in the diet. This difference in manner of administration might conceivably have had an effect on the results and furthermore, the use of ethanol as a solvent for 8-nitroquinoline in this experiment, may have influence the metabolism of 8-nitroquinoline and therefore the incidence of tumor development. It has been reported that ethanol inhibited diethylnitrosamine induced hepatomas and it seems likely that alcohol might influence the metabolism of diethylnitrosamine (Habs et al., 1976). A similar mechanism should be considered in the present results in hamsters although the available knowledge on the interaction of ethanol with 8-nitroquinoline at the cellular or tissue level dose not allow an explanation of the lack of carcinogenicity observed.

Since 8-nitroquinoline is only slightly soluble in water and dissolves much more readily in alcohol, this necessitated administration by way of an alcohol medium. However, the concentration given, a 0.05% solution, was limited by the problem of solubility. Possibly the use of higher concentrations in the diet might lead to alternative results. Despite this consideration oral administration of 0.05% 8-nitroquinoline in this experiment has been clearly shown not to increase the incidence of tumors in Syrian golden hamsters.

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