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Tumor Frequency and Characteristics after a Single Dose of Dimethylnitrosamine or Diethylnitrosamine in Partially Hepatectomized Rats


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Summary. Two groups of 75 rats were injected intraperitoneally with one single dose of 9 mg/kg DMNA and 120 mg/kg DENA, respectively, 28 h after partial hepatectomy. Control groups of non-hepatectomized rats received one single injection of DMNA or DENA at doses of 20 mg/kg and 200 mg/kg, respectively, which were found to be equitoxic to the doses administered to partially hepatectomized rats. One control group of partially hepatectomized rats was injected with saline. Tumors developed in the partially hepatectomized rats injected with nitrosamines with the following frequency: for DMNA: 13% in the liver, 13% in kidney, 4% in lung, 4% at the surgical scar, 9% in hematopoietic tissue and 13% in other organs; for DENA: 11% in liver, 27% in the kidney, 2% at the surgical scar, 2% in hematopoietic tissue, and 11% in other organs. The histological characteristics of these tumors are described. Statistical analysis of the results shows that no significant difference exists in the overall tumor incidence induced by DMNA and DENA and that the difference between liver and kidney tumors induced by DENA is significant, whereas the difference between DMNA- and DENA-induced kidney tumors is less significant. When analyzed by t-test, our results show that death from tumors occurred at an earlier time after DENA than after DMNA treatment and that liver tumors appeared at a significantly earlier time after DENA than after DMNA treatment. Tumors appearing in the same experimental group display similar mean induction times.

The possible correlation between metabolic half-life of each nitrosamine in the body and their respective carcinogenic power is discussed.

The longer half-life of DENA may be responsible for the shorter tumor induction time observed for this drug, compared to DMNA. The liver tumor incidence, on the other hand, seems to be independent of the half-life but strongly determined by the fact that the proximate carcinogen reaches the hepatic cell during the DNA synthesis phase.
Introduction

Dimethylnitrosamine (DMNA) and diethylnitrosamine (DENA) are powerful carcinogens for most animal species tested so far (Montesano and Magee, 1974). Their carcinogenic properties depend upon metabolic activation processes which occur mainly in liver (Magee and Barnes, 1967), at a similar rate in the rat for both compounds (Heath, 1962), and which result in alkylation of macromolecules. Alkylation of nucleic acids occurs mainly on the N7 position of guanine (Magee and Farber, 1962) although other sites, quantitatively less important though perhaps functionally essential, have also been identified (Lawley et al., 1968).

The relationship between alkylation level and cancer induction is not clear. After administration of a single dose of DMNA or DENA, liver DNA contains a higher amount of alkyl groups than any other organ DNA (Swann and Magee, 1968, 1971). However, tumor appears only in kidney after one single dose of DMNA (Magee and Barnes, 1962) whereas DENA might induce some liver tumors (Craddock, 1975a). On the other hand, only chronic administration of nitrosamine is capable to induce a high number of liver tumors (Magee and Barnes, 1967).

There seems to be a relationship between the low mitotic activity of normal rat liver and its resistance to chemically induced carcinogenesis. Indeed, when administered to partially heptectomized rats, one single dose of carcinogenic nitroso-compounds does induce liver tumors (Craddock, 1971, 1973a, b, 1975a; Craddock and Frei, 1974; Pound and Lawson, 1975).

However, previous work on carcinogenesis by nitrosamines administered to partially heptectomized rats has usually been performed on rather small numbers of animals, and a clear distinction between groups receiving different treatments has not always been made.

In order to obtain results endowed with statistical significance, we decided to study this problem on a sufficiently large number of animals.

The interest of an accurate comparison of the relative carcinogenic powers of DMNA and DENA lies in the fact that DENA, being less toxic than DMNA, can be administered in much higher doses and therefore persists for a longer time in the body. The question, then, is to see whether this longer persistency would result in a broadening of the organotropism of the drug, as regards tumor induction.

Our results show that, besides an important number of kidney tumors, DMNA and DENA induce liver tumors, when administered after partial heptectomy, DENA displaying a shorter mean induction time. DMNA also induced some tumors in less usual target organs: hematopoietic tissues, thymus, and adrenal glands.

Materials and Methods

Chemicals

DMNA and DENA were purchased from Schuckard and kept at $-20^\circ$ C in the dark. Both nitrosamines were used without further purification and were diluted with saline just prior to injection. Thymidine-6-$^3$H (specific activity 8 Ci/mmol) was purchased from I.R.E. (Belgium).