The Effect of 1-Methoxypropylpropynitrosamine in Syrian Golden Hamsters*

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Summary. The carcinogenicity of the \( \alpha \)-dipropynitrosamine (DPN) methylether, 1-methoxypropylpropynitrosamine (1-MPPN), was investigated in Syrian hamsters for comparison with the effect of the \( \alpha \)-DPN acetylester, 1-acetoxypropylpropynitrosamine (1-APPN). It seemed possible that 1-MPPN, 1-APPN and DPN could form a common intermediate. However, contrary to the effect of 1-APPN, no tumors were found at the injection site after subcutaneous 1-MPPN treatment. The main target organ for 1-MPPN was the respiatory tract (as with DPN) and the lungs were greatly affected. In addition, pharyngeal and forestomach tumors occurred, and these were not observed after DPN administration. The results of 1-MPPN treatment, relative to DPN and 1-APPN, are discussed.

Die Wirkung von 1-Methoxypropylpropynitrosamin bei Syrischen Goldhamster


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Introduction

Induction of neoplasms by subcutaneously administered 1-acetoxypropylpropynitrosamine (1-APPN) at the injection site (Althoff et al., 1976) led us to assume the local effect was due to formation of an α-hydroxylated dipropynitrosamine (Druckrey et al., 1967, 1975; Magee, 1967) by simple hydrolysis or ubiquitous esterases. Similarly, 1-methoxypropylpropynitrosamine (1-MPPN) could also undergo α-hydroxylation of the propyl sidechain or such an intermediate could also be formed by non-specific O-demethylases; the latter has been described in various tissues (Smith et al., 1975; Burke and Upshall, 1976). Therefore 1-MPPN was synthesized and examined in Syrian golden hamsters as part of a continuing comparative study, using equitoxic dose levels and subcutaneous routes of administration.

Material and Methods

Eight-week-old Syrian hamsters from the Eppley colony were housed in groups of 5 by sex in plastic cages. They were maintained under standard conditions (21 ± 1 °C, 55 ± 5% humidity, 10 × air change per hour) and received a pelleted diet (Wayne, Allied Mills, Chicago, Ill. USA) and water ad libitum. The animals were weighed once weekly.

The acute toxicity of 1-MPPN was determined by Weil's method (1952). Groups of 5 male and 5 female hamsters received a single subcutaneous (s.c.) injection of either 250, 500, 1000 or 2000 mg/kg body weight (b.w.). The mortality during an 8-day observation period was used as a parameter. Survivors were kept for life.

To examine the chronic effect of 1-MPPN, hamsters (15 female and 15 male hamsters per group) were treated s.c. once weekly for life at dose levels of 60, 30, and 15 mg/kg b.w. (the 30 mg treatment group had 20 male hamsters). Controls received olive oil solvent only. Animals were killed when moribund (durations stated are from the beginning of treatment). After animals were completely autopsied, organs were fixed in 10% buffered formalin and bones were decalcified (D-Calcifier, Lerner Labs, Stamford, Connecticut, USA). After paraplast embedding, step sections (5-10) were prepared from the nasal cavities, including the palate, larynx, trachea with attached stem bronchi, lungs, pancreas, urinary bladder with rectum and vagina, or Cowper's gland and prostate. Sections were stained with hematoxylin and eosin.

All chemicals used in the synthesis of 1-MPPN were reagent grade. 1-MPPN was prepared from propyldinepropyline, essentially by the method of Wiessler (1974). The imine was prepared by condensing n-propylamine with propionaldehyde under basic conditions and was distilled from potassium hydroxide. The final product, 1-MPPN, was distilled (b.p.; 79 — 80 °C 14 mm Hg) and analyzed for purity by gas-liquid chromatography (GLC), thin-layer chromatography (TLC) and elemental analysis. The conditions and results of the analyses were: GLC, 2-m column of 15% DEGS on Chromasorb W-HP, 150 °C, flow; 20 ml/min, under which a single component with a retention time of 3.7 min was observed. TLC [silica gel developed with hexane/diethyl ether/methylene chloride (4:3:2 v/v)] also showed a single component. Elemental analysis-calculated: C, 52.48, H, 10.07, N, 17.49, O, 19.96; determined: C, 52.44, H, 10.14, N, 17.44, O, 19.98. On the basis of these analyses, the product was estimated to be 99.4% 1-MPPN.

Results

The LD50 of 1-MPPN in Syrian hamsters after s.c. administration was 583 mg/kg b.w.; 458 for females and 707 mg/kg b.w. for males. Generalized hyperemia, focal hemorrhage and necrosis were seen in thoracic and abdominal organs of hamsters in the high dose level groups. In the low dose level groups, 19 hamsters survived the 8-day observation period, but died in the following 2-6 weeks. One of these hamsters had a tracheal papillary polyp (at 6 weeks).