Cancer Chemother Pharmacol (1982) 10:70–71

Cancer Chemotherapy and Pharmacology

Vinylchloride: Decomposition Product of BCNU in vivo and in vitro

Michael R. Clemens[1], Hartmut Frank[2], Herbert Remmer[2], and Hans Dierck Waller[1]

[1] Department of Internal Medicine II and
[2] Institute for Toxicology, University of Tübingen, D-7400 Tübingen, Federal Republic of Germany

Summary. *Vinylchloride (VC) was identified by gas chromatography-mass spectrometry as a decomposition product of 1,3-bis-(2-chloroethyl)-1-nitrosourea (BCNU). VC was observed in blood and exhaled air from patients after administration of BCNU. Production of VC is evident even after incubation of blood from normal donors with BCNU.*

Introduction

Nitrosoureas decompose in physiological conditions to alkylating and carbamoylating moieties [4]. The relative contributions of these chemical reactivites to toxic and therapeutic effects are only partly known. It is suggested that 1,3-bis-(2-chloroethyl)-1-nitrosourea (BCNU) cleaves at the bond between the nitrosamino and the carbonyl groups, leading to the intermediate formation of chlorethyl isocyanate. 2-Chlorethylamine hydrochloride, acetaldehyde, nitrogen, and carbon dioxide were identified as decomposition products of BCNU in aqueous solution [1]. In this paper we report the occurrence of an additional metabolite of BCNU, i.e., vinylchloride (VC). This metabolite was detected in blood and exhaled air from patients treated with BCNU. The present results yield additional data concerning pharmacological and biological activities of BCNU.

Methods

Vinylchloride was identified by gas chromatography and gas chromatography-mass spectrometry (GC-MS). Gas chromatography was performed on Porasil C as previously described [2]. The retention time of VC is 14.5 min. GC-MS analysis was performed in a Finnigan instrument (model 4020), with a Porasil C-packed column (5 m × 3 mm) at 60° C isothermal, with helium (30 ml/min) as carrier gas. The interface, a one-stage all-glass jet separator, was maintained at 80° C. The ion source was kept at 200° C, electron energy 40 eV, and multiplier 1.5 kV.

Five patients suffering from plasmocytoma were examined for formation of VC. BCNU was administered IV in dosages of 1 mg/kg body weight (range 60–80 mg) at a constant rate over 15 min. At predetermined times during infusion 4-ml blood samples were taken, 1 ml citrate being added to each as anticoagulant. In each case, 3 ml of the blood was immediately placed in 10 ml head space vials. After 30 min of equilibration at room temperature 1 ml of the head space was injected into the gas chromatograph and analysed for VC. Concurrently exhaled air samples from the patient were collected in special bags, after which 10 ml of breath was injected into the gas chromatograph and checked for VC. VC was undetectable in the room air. For calibration VC was determined in the head space above blood from untreated, healthy subjects and containing appropriate amounts of VC.

For the in vitro study freshly drawn blood from healthy persons with citrate as anticoagulant was washed three times with saline, after which 3 ml of red cell suspension was placed in 10 ml head space vials and BCNU (75 μM) was added. After incubation for predetermined periods at 37° C, 1 ml of the head space was analysed for VC by gas chromatography.

Results and Discussion

During the infusion of BCNU the average concentration of VC in the head space over blood from the patients amounted to 0.02 nMol/ml blood (range 0.011–0.037 nMol/ml blood) collected after 15 min. Comparable results were obtained after 5 and 10 min.

VC was estimated in the exhaled air at an average concentration of 0.02 ppm (range 0.011–0.033 ppm) after 15 min of infusion. Comparable amounts were measured after 10 min and smaller amounts (mean 0.013 ppm) after 5 min.

Montgomery [4] has shown that the vinyl carbonium ion is an aqueous decomposition product of BCNU, and suggested

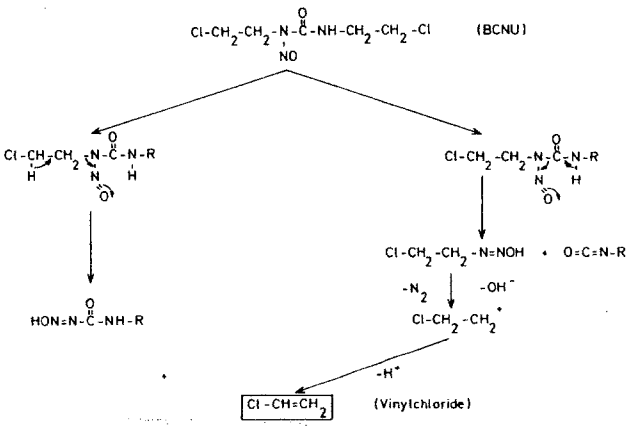

Fig. 1. Possible pathways leading from BCNU to VC

Reprint requests should be addressed to M. R. Clemens

0344-5704/82/0010/0070/$ 01.00

its possible biological activity. We did not observe a spontanous formation of VC when BCNU was incubated in saline or in plasma at 37° C. However, VC was produced during incubation of erythrocytes from normal donors with BCNU at an average concentration of 14.6 ± 3 nMol/10^{12} erythrocytes (mean ± SD, $n = 5$) within 15 min. These results suggest that red cells catalyse the decomposition of BCNU to VC.

Vinylchloride is an agent with mutagenic potency [3]. Biological effects are dependent upon its metabolic activation. It is likely that a microsomal mixed-function oxidase, which is the major target organ for the carcinogenicity of VC in humans, efficiently converts this procarcinogen into a reactive intermediate in vitro. The resulting epoxide is able to react with macromolecules of cells, e.g., DNA.

References

1. De Vita VT, Denham C, Davidson JD, Oliverio VT (1967) The physiological disposition of the carcinostatic 1,3-bis-(2-chlorethyl)-1-nitrosourea (BCNU) in man and animals. Clin Pharmacol Ther 8: 566–577
2. Frank H, Hintze T, Biboes D, Remmer H (1980) Monitoring lipid peroxidation by breath analysis: endogenous hydrocarbons and their metabolic elimination. Toxicol Appl Pharmacol 56: 337–344
3. Garro AJ, Guttenplan JB, Milvy P (1976) Vinyl chloride-dependent mutagenesis: effects of liver extracts and free radicals. Mutat Res 38: 81–88
4. Montgomery JA (1976) Chemistry and structure activity studies of the nitrosoureas. Cancer Treat Rep 60: 651–664

Received August 17/Accepted September 27, 1982