

Comparison of the carcinogenic potential of streptozotocin by polarography and alkaline elution^{*}

C. COJOCEL¹, L. NOVOTNY², A. VACHALKOVA³, B. KNAUF⁴

¹Faculty of Medicine, e-mail: cojocel@hsc.kuniv.edu.kw, and ²Faculty of Pharmacy, Kuwait University, Safat 13110, Kuwait; ³Cancer Research Institute, Slovak Academy of Science, 83391 Bratislava, Slovak Republic; ⁴Aventis, Aventis Pharma Deutschland, 65812 Bad Soden a. Ts., Germany

Received October 29, 2002

The carcinogenic potential of streptozotocin (STZ) was evaluated by the polarographic determination of its reduction potential in the presence of α -lipoic acid and detection of DNA single-strand breaks by alkaline elution. After STZ electrochemical reduction in an anhydrous solvent, the half-wave potential ($E_{1/2}$) was determined to be -1.340 V. The parameter of the carcinogenic potential ($\text{tg } \alpha$) for STZ was 0.400. This is in good agreement with WHO data regarding STZ carcinogenicity. Additionally, it is in the good agreement with the $\text{tg } \alpha$ value determined for the positive control used, N-nitroso-N-methylurea (NMU), which was found to be 0.459.

The 3 hours exposure of A549 human lung tumor cells to 250, 500, and 1000 nmol/ml STZ was followed by DNA single-strand breaks detection using the alkaline elution method. NMU, the positive control, was tested under identical experimental conditions at the same concentrations. Without metabolic activation, NMU induced a significant formation of DNA single-strand breaks only at 1000 nmol/ml. In the presence of the metabolic activation, NMU caused a significant, concentration-dependent formation of DNA single-strand breaks. In the absence of metabolic activation, STZ induced no significant formation of DNA single-strand breaks at any concentration used. In the presence of metabolic activation, STZ caused a significant, concentration-dependent formation of DNA single-strand breaks.

The results of this study underline the crucial role of using a metabolic activation system when carcinogenic potential of drugs and chemicals is investigated *in vitro* studies. Results of polarographic experiments and alkaline elution correlate well with each other and they indicate that these methods are useful to early predict the carcinogenic potential of STZ and other xenobiotics.

Key words: Streptozotocin, polarography, alkaline elution, single-stranded DNA, carcinogenicity.

Streptozotocin (2-Deoxy-2[[methyl-nitrosoamino)carbonyl]amino]-D-glucopyranose, CAS No.18883-66-4) (STZ) is an antibiotic originally derived from the soil micro-organism *Streptomyces achromogenes*.

The principal therapeutic use for STZ is in the treatment of metastasizing pancreatic islet cell tumors. It is also effective in treating malignant carcinoid tumors, especially of the small intestine. It has been investigated for use in diabetes,

since it has specific toxic action on pancreatic beta-cells. Moreover, the compound has been shown to artificially induce diabetes in rats [4]. STZ has been investigated as a potential antibacterial agent but has never been used commercially for this purpose. There is evidence for the carcinogenicity of STZ in several experimental animal species [9, 10]. No adequate data on humans are available (group 2B), but the chemotherapeutic use of STZ indicates the existence of an exposed group. Routes of potential exposure to STZ are inhalation, injection and dermal contact. Health professionals such as pharmacists, doctors and nurses may be exposed. Potential occupational exposure may also occur during STZ production.

The aim of the present study was to evaluate the carcino-

^{*}This study was supported by Kuwait University Research Grant No. PC 02/99 and Grant No. 7048/22 from the Grant Agency for Sciences (VEGA), Slovakia.