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Kinetics of Butaperazine Adsorption onto Quartz Cells

Keyphrases □ Butaperazine—adsorption onto quartz cells, kinetics □ Adsorption—butaperazine onto quartz cells, kinetics □ Tranquilizers—butaperazine, adsorption onto quartz cells, kinetics

To the Editor:

Kinetics of adsorption of drugs onto plastic and filtering materials are well documented (1–7). However, kinetics of adsorption of drugs onto quartz cells appear to be rarely reported. During our study on the interaction between butaperazine, an antipsychotic agent, and a saliva-stimulating device[1], we found that the fluorescent intensity of the butaperazine solution in cyclohexane stored in quartz cells decreased with time. Additional studies were carried out to explore this interaction, and the results of these preliminary studies are reported here.

The stock solution (2 mg/ml) of butaperazine maleate[2] was prepared in 95% ethanol. This solution was diluted with cyclohexane[3] in 100-ml volumetric flasks to concentrations of 2.0 and 0.14 μg/ml. Then 1 ml of 1 *N* NaOH solution was added, and the flasks were shaken to convert butaperazine maleate to its free base in cyclohexane. The cyclohexane was transferred immediately and directly into three quartz cells, which were then covered with lids.

Fluorescent intensities were measured immediately and every 5 min thereafter for 30 min with a fluorometer[4] at the excitation wavelength of 312 nm and the fluorescent wavelength of 498 nm. The average results, expressed in terms of percent of the initial fluorescent intensity as a function of time, are shown in Fig. 1. In the study with the higher initial concentration, the fluorescent intensity decreased to a constant 88% after 10 min. The decrease in intensity with the lower initial concentration followed an apparent first-order process with a half-life of 16 min.

These concentration-dependent decrease phenomena are consistent with the saturable adsorption theory. This contention is also supported by the following desorption study. Two cells were filled with 2 μg/ml of the butaperazine solution. After 10 min of adsorption equilibration, the solution in the cell was discarded and the cell was filled with pure cyclohexane. The fluorescent intensity of the solution was then measured as a function of time. The average results are also shown in Fig. 1. The average recovery into the fresh cyclohexane at 30 min was about 33%.

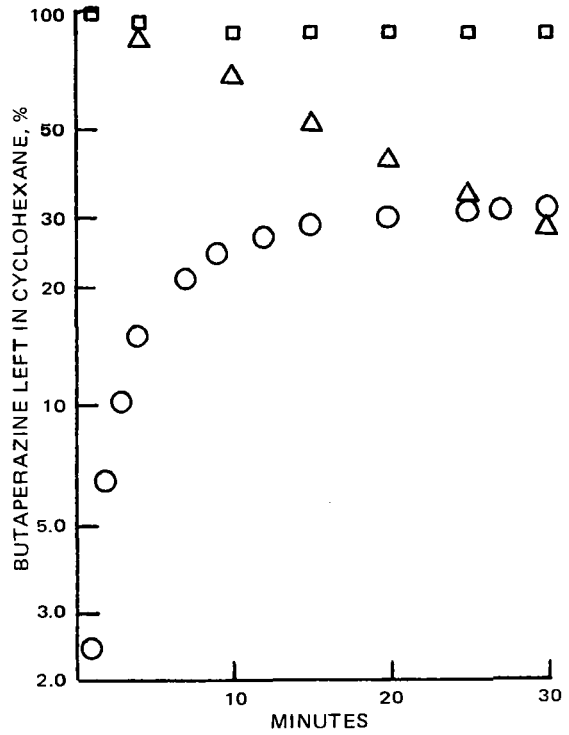

Figure 1—*Time course of the fluorescent intensity of cyclohexane solutions of butaperazine in the cell. Key:* □, *initial concentration of 2.0 μg/ml in the adsorption study;* △, *initial concentration of 0.14 μg/ml in the adsorption study; and* ○, *desorption study where the scale 100 is equivalent to 0.22 μg/ml when all adsorbed butaperazine was desorbed into cyclohexane.*

In all of these studies, the butaperazine solutions were protected from light irradiation whenever feasible. Adsorption of butaperazine onto the glassware was mentioned in one (8) of two recent papers (8, 9) describing similar fluorometric methods for the measurement of butaperazine concentrations in plasma. Moreover, in the present study, coating the cells with silicone[5] was ineffective in reducing the adsorption effect.

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[1] Parafilm, American Can Co., Neenah, Wis.
[2] A. H. Robins Co., Richmond, Va.
[3] Certified ACS grade, Fisher Scientific Co., Fair Lawn, N.J.
[4] Perkin-Elmer model 203 fluorescence spectrometer, Norwalk, Conn.
[5] Siliclad, Clay Adams, Division of Becton, Dickinson and Co., Parsippany, NJ 07054

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Differing Antitumor Activities of the Hydrochloride and Methiodide Salts of 1-Ethyl-3-(3′-dimethylaminopropyl)-carbodiimide

Keyphrases □ 1-Ethyl-3-(3′-dimethylaminopropyl)carbodiimide—hydrochloride and methiodide salts, antitumor activity compared, mice □ Antitumor agents, potential—1-ethyl-3-(3′-dimethylaminopropyl)carbodiimide, hydrochloride and methiodide salts compared, mice

To the Editor:

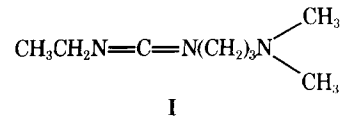
Cellular surface modifications effected by the reaction of mouse neuroblastoma C1300 and carcinoma TA3 cells with 1-ethyl-3-(3′-dimethylaminopropyl)-carbodiimide hydrochloride (II) have been demonstrated *in vitro* to result in an increased susceptibility of these cells to immune lysis by soluble antibodies (1). This carbodiimide derivative also has been shown to exert an *in vivo* antitumor activity. On the basis of the following lines of evidence, this activity appears to result from an enhanced host immune reactivity against drug-modified tumor cells:

1. Chemotherapeutic effectiveness against neuroblastoma C1300 solid tumors increases with increasing host levels of cytotoxic serum antibodies (1).

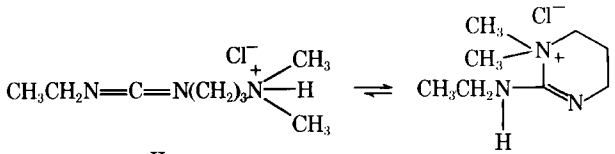
2. Drug inhibition of TA3 ascites carcinoma growth is not observed in hosts that have received an immunosuppressive 700-rad whole body dose of cobalt-60 radiation (2).

In addition to having chemotherapeutic potential, the *in vivo* action of this carbodiimide derivative may be useful for tumor diagnosis using the scintillation camera, since the enhancement of host immune reactions in neoplastic tissue could create a favorable condition for the selective uptake of radioisotopically labeled compounds (3).

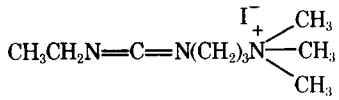
On the basis of NMR and IR evidence, the water-soluble hydrochloride salt[1] (II) of the carbodiimide base 1-ethyl-3-(3′-dimethylaminopropyl)carbodiimide (I) has been found to exist in aqueous solution at physiological pH as an equilibrium mixture of two isomeric species: 7.4% open chain carbodiimide hydrochloride (II*a*) and 92.6% 2-ethylamino-3,3-dimethyl-3,4,5,6-tetrahydropyrimidine chloride (II*b*) (4, 5). Because of the structural complexity introduced by isomerism of II, we synthesized and tested the chemotherapeutic activity of the water-soluble carbodiimide salt 1-ethyl-3-(3′-dimethylaminopropyl)carbodiimide methiodide (III), which is formed by reaction of I with methyl iodide (4).



I



II*a* II*b*



III

NMR and IR studies showed that III exists exclusively as the open chain carbodiimide at physiological pH (5). From a comparison of the biological effects of II and III, we sought to gain evidence as to whether the structural features of II—apart from its chemically reactive carbodiimino functionality—are important factors in the antitumor action exerted by this compound.

In vitro cytotoxicity assays were carried out to assess the relative abilities of II and III to increase the complement-dependent (6) antibody-mediated lysis of neuroblastoma C1300 target cells. The antiserum used was drawn from A/HeJ mice[2] bearing 21-day-old neuroblastoma C1300 tumors. The antiserum was added to test cultures so that the final dilution was 1:640 (v/v). Rabbit serum was absorbed with C1300 cells by the method of Boyse *et al.* (7) to remove naturally occurring toxic substances (8); the absorbed rabbit serum was then placed in test cultures at a final dilution of 1:40 (v/v) as a source of the complement.

Lysis of C1300 target cells was determined from the percentage release of the intracellular chromium-51 label during an 8-hr incubation at 37°. The method used to label C1300 target cells with chromium-51, the preparation of the antiserum and complement, and details of the cytotoxicity assay procedure were described previously (1). Compounds II and III were added to test cultures at an identical concentration of 0.16 m*M*. On the basis of drug tolerance studies, this concentration of carbodiimide was determined to be the maximum that was not toxic to C1300 cells over the 8-hr incubation used in all cytotoxicity assays.

Results of *in vitro* cytotoxicity assays are summarized in Table I. Neuroblastoma C1300 target cell lysis by A/HeJ immune serum increased significantly when II was added to test cultures (from 13.4 to 27.8%). Addition of the open chain carbodiimide III, however, did not lead to increased target cell immune lysis.

[1] Ott Chemical Co., Muskegon, Mich.

[2] Jackson Laboratory, Bar Harbor, Me.