Antibiotic Activity of Deoxy-Herqueinone (Atrovenetin Monomethyl Ether)

Atrovenetin was first isolated from cultures of *Penicillium atrovenetum* (G. Smith)[1], and subsequently from cultures of the closely related species *Penicillium herquei* (Bainer and Sartory)[2], along with the closely related compounds herqueinone and norherqueinone. The antibiotic activity of cultures of *P. herquei* was shown to be mainly due to the single component atrovenetin[2]. The conversion of herqueinone and norherqueinone to deoxyherqueinone and deoxy-norherqueinone, and the identity of the latter with atrovenetin, was reported by BARTON et al.[3]. Accordingly deoxy-herqueinone should be a monomethyl ether of atrovenetin. In view of the antibiotic activity of atrovenetin, the activity of deoxyherqueinone has now been investigated; it is found to be active against a number of organisms, though to a lesser degree than atrovenetin[4]. Both herqueinone and norherqueinone are found to be completely inactive, while the deoxy derivatives prepared from them are active. The relative activities of atrovenetin and deoxy-herqueinone are given in the Table.

Organism tested	Min. inhibitory concentrations mcg/ml Atrovenetin 4	Deoxyherqueinone
B. mycoides	0.4	20.0
B. subtilis	0.5	18.0
S. lutea	0.6	35.0
S. aureus	0.7	20.0
Streptomycin resistant strain gram + ve rods of sublitis group	0.9	18.0
Penicillin resistant *Staphylococcus aureus*	0.7	20.0
K. pneumoniae	0.3	No activity

Zusammenfassung. Aus Herqueinon erhält man Desoxyherqueinon (Atrovenetin-monomethyl-äther) mit antibakteriellen Eigenschaften. Spektrum ähnlich wie Atrovenetin, obwohl die minimale Hemmungskonzentration höher liegt.

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Thiopental Binding to Serum Albumin

Most drugs interact with one or more plasma proteins which may influence pharmacological activity. Albumin is the protein component of plasma most often involved in the binding of various substances[1]. The prolongation of sleep with thiopental compared with hexobarbital is caused by the former being more strongly bound to plasma protein[2]. The percentage of binding of barbiturates with protein has been reported elsewhere[2,3]. In this study the number of binding sites of thiopental on bovine serum albumin has been determined. In addition the effect EDTA (disodium ethylenediamiotetraacetate) has on thiopental binding has been studied.

Method. The equilibrium dialysis technique described by KLOTZ[4] using bovine serum albumin (Biochemical Research, Cohn Fraction Grade C) was used for this experiment. Dialysis was carried out in 22 · 150 mm test tubes with $^5/_8$ inch dialysis membranes first soaked in 0.1 *M* nitric acid to remove impurities[5] and then suspended against solutions of various concentrations of thiopental in 0.1 *M* tris hydrochloride-tris buffer (pH 7.42) at 7°C for 12 h. Concentrations of thiopental ranged from $7.0 \cdot 10^{-4} M$ to $5 \cdot 10^{-5} M$ and bovine serum albumin was used at a concentration of 0.05 Gm/100 ml ($7.25 \cdot 10^{-6} M$).

The experimental data were analyzed by means of the Scatchard equation[6], $\bar{v}/A = kn - k\bar{v}$; where $\bar{v}$ is the molar ratio of bound thiopental molecules to albumin, A is the free thiopental concentration in *M*, k is the average apparent association constant for binding, and n is the average maximal number of binding sites on albumin. The ratio of $\bar{v}$ to A was determined from the values obtained for bound thiopental at given concentrations of thiopental. If all binding sites are equivalent and independent, plots of $\bar{v}/A$ as a function of $\bar{v}$ will produce a straight line. The intercept on the $\bar{v}/A$ axis is kn, when $\bar{v}$ approaches 0 and the intercept on the $\bar{v}$ axis is n, when $\bar{v}/A$ approaches 0 (Figure).

Results. The results shown in the Figure demonstrate a linear relationship between $\bar{v}/A$ and $\bar{v}$ and that the binding sites are equivalent and independent. As shown in the Figure the average maximal bound thiopental with bovine serum albumin was determined roughly by extrapolating the line to $\bar{v}/A$ axis. The value of kn was 50,000, n was 5 and k was 12,000. Calculated $-\Delta F°$ was approximately 5300 cal/mole.

The effect of EDTA on the binding of thiopental to serum albumin is also shown in the Figure. There is a decreased capacity for thiopental binding on albumin in the presence of EDTA in the system. Values determined from our data were: n = 4, kn = 40,000, and k = 10,000. Free energy was 5100 cal/mole.

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