when clinical trials of partially ionized drugs are being considered for different countries.

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Effect of actinomycin D on the recovery of cardiac noradrenaline after depletion with guanethidine

It has been suggested that the recovery of tissue noradrenaline levels after reserpine depletion is dependent upon the synthesis of new storage vesicles in the cell body and their subsequent transport down the axons to the nerve terminals (Dahlström, 1965; Dahlström & Haggendal, 1966). Evidence for such a suggestion comes from studies showing that fresh vesicles begin to reach the nerve terminals within 24 h after reserpine administration (Dahlström, 1967). Prolongation of the recovery of tissue noradrenaline in reserpine-treated animals by agents which inhibit protein synthesis, such as actinomycin D or SKF-525A (β-diethylaminoethyldiphenylpropyl acetate), is consistent with this hypothesis (Mueller & Shideman, 1968). Guanethidine in addition to producing pharmacological effects different from those of reserpine, has been shown to produce depletion of noradrenaline stores by a mechanism that appears to be, at least in part, similar to the one mediated by reserpine, i.e. by blocking of the granular pump (Shore & Giachetti, 1966). It was therefore of interest to determine the effect of actinomycin D on the recovery of cardiac noradrenaline after depletion with guanethidine.

Male Sprague-Dawley rats weighing 125 to 150 g were injected i.p. with 20 mg/kg of guanethidine, a dose which has been shown to produce over 90% depletion of cardiac noradrenaline (Westfall & Osada, 1968), and 48 h later half of these rats were treated with actinomycin D (100 μg/kg,i.p.). The animals not receiving actinomycin D were injected with a comparable volume of saline. Since actinomycin D has been shown to reduce food consumption, a paired feeding technique similar to that of Mueller & Shideman (1968) was used. The quantity of food eaten by each experimental animal on one day was given to its control on the following day. Animals were killed by decapitation at 6 h, 3 days, 4 days and 6 days after guanethidine. The hearts were removed and analysed for endogenous noradrenaline according to the trihydroxyindole procedure of Euler & Lishajko (1961).

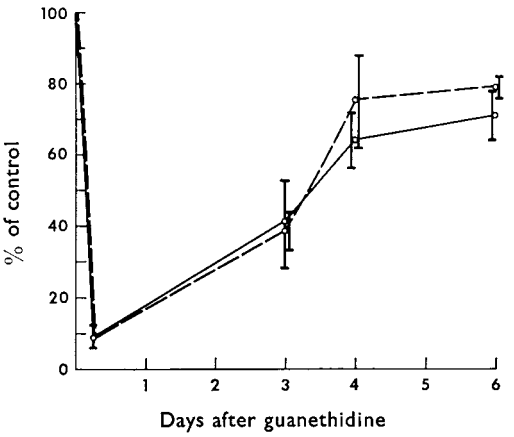

FIG. 1. The influence of actinomycin D on the recovery of myocardial noradrenaline levels after guanethidine. Guanethidine was administered in a dose of 20 mg/kg i.p. and 2 days later half of the rats were injected with actinomycin D at a dose of 100 μg/kg i.p. Data are plotted as % of control level ± standard error of the mean *vs* time in days. Each point represents the mean from at least 4 animals. ——; guanethidine alone. – – – –; guanethidine and actinomycin D.

In these experiments, no difference was found in the recovery of heart noradrenaline in animals receiving the antibiotic and the controls (Fig. 1). These experiments, therefore, fail to provide evidence that resynthesis of storage vesicles is a necessary requirement for repletion of noradrenaline stores following depletion with guanethidine. Thus, either the mechanism by which guanethidine causes depletion of noradrenaline differs, in some way, from the depletion brought about by resperpine, even though both drugs appear to inhibit transport across the granular membrane, or a reversal of guanethidine-induced inhibition of noradrenaline transport by storage granules is produced before new storage vesicles can be synthesized and transported to the nerve terminals.

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