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SHORT COMMUNICATIONS

Reducing toxic effects of benzylpenicillin by modifying the metabolic capacity of the reticulo-endothelial system

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STUDIES carried out on the mechanism of toxicity of benzylpenicillin implicate a variety of factors such as the formation of substance with toxic effect, the modification of intestinal microbian flora or toxins produced by pathogenic microbes upon which the antibiotic exercises its effect.[1-4] In the following study the role of hepatic reticulo-endothelial (RES) in the toxicity of benzylpenicillin has been studied.

MATERIALS AND METHODS

The investigations were carried out on 480 H-strain, male mice, weighing 18–22 g and on 60 dogs of 10–16 kg. The hepatic RES was blocked by i.v. administration of 10% colloidal solution of India ink in doses of 0·2 ml/animal, 48 hr before the administration of benzylpenicillin. The MTD of benzylpenicillin was 250 mg/kg mice. Reticulin (obtained from Biofarm, Bucharest) was administered in doses of 0·2 ml/mouse.

The substance stimulates the functions of the reticulo-endothelial tissue, prevents and reduces the increased permeability of the capilars, determinated by hystamine.

The function of the RES in the storage capacity of the liver in dogs was studied under various experimental conditions, by measuring the benzylpenicillin concentration in the blood at intervals of 1, 2 and 4 hr. Substances were administered in the following doses: benzylpenicillin 10·0 units/kg i.m., Reticulin 0·2 ml/kg s.c., India ink 10% colloidal solution 1·5 ml/kg i.v. Experiments were carried out with a group of 40 mice and 12 dogs. Statistical interpretation of the results (Student's *t* test) are shown in Figs. 1 and 2.

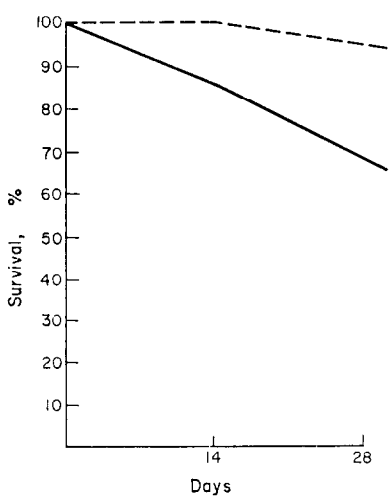

FIG. 1. Toxicity of benzylpenicillin in mice. Each point represents 4 experiments; 40 mice in each group for each determination.
—— India ink and penicillin; – – – Reticulin, India ink and penicillin.

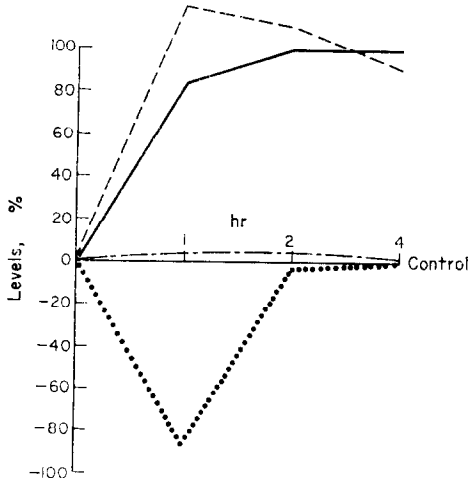

FIG. 2. Blood levels of penicillin in dogs; 12 dogs in each group.
—— India ink; – – – Reticulin and India ink; — · — · India ink and Reticulin; · · · · Reticulin.

RESULTS

For H strain of mice the LD_{50} dose of benzylpenicillin was 329 mg/kg, with limits between 260·7–363·1 mg/kg. Taking this into account a single dose of 250 mg/kg (MTD) was administered to mice. This single dose had no lethal effect during the 28 days of observation. On animals in which the RES was blockaded with India ink the 250 mg/kg dose lead to a lethal effect of 33 per cent towards the end of the observation period. On animals that were submitted to a 5-day-treatment of Reticulin before blockading a 250 mg/kg dose of benzylpenicillin has a reduced lethal effect of 5 per cent (Fig. 1).

Determinations in dogs were carried out to establish more accurately the function of hepatic RES in the storage of benzylpenicillin. Concentrations of benzylpenicillin in the blood were determined at intervals of 1, 2 and 4 hr on normal dogs and on dogs under India ink treatment or India ink and Reticulin administration.

In dogs given India ink blood level increased up to 100 per cent and extended for 4 hr. With 5-day-treatment with Reticulin prior to India ink administration blood levels of benzylpenicillin increased still more. If Reticulin was administered to animals given India ink 2 hr before the penicillin dose, the blood level of penicillin approached control. If Reticulin is given to normal animals 2 hr before penicillin the penicillin level, after 1 hr is 80 per cent lower.

These experiments show that hepatic RES intervenes in the metabolism of benzylpenicillin. Stimulation of the storage capacity of RES through Reticulin reduces the toxicity of benzylpenicillin treated animals which have been blockaded with India ink.

Experiments on dogs show that this is most probably due to a process of storage of benzylpenicillin in the hepatic RES. A decrease of the antibiotic was obtained through stimulation of the RES by a single dose of Reticulin. It is to be noted that in dogs, due to a functional particularity of the RES repeated (5 days) administration of Reticulin leads to a superloading of the RES. This causes an increased blood level of penicillin.

Pharmacological Department,
Chemical-Pharmaceutical Research Institute,
Bucharest 4,
Rumania

M. TIMAR
A. BOTEZ
C. M. GEORGESCU
V. IANCU
I. NITELEA

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Studies on the role of the liver component of reticulo-endothelial system (RES) in the metabolism of sulfametoxipiridazine and sulfametoxipirimidine

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THE long acting sulfonamides are of great importance in therapeutics but their secondary toxic effects have to be guarded against in their clinical applications.[1–6] Knowing the stress to which the RES undergoes in pathological processes in which the sulfonamidetherapy is applied, we undertook to study this morpho-functional system as related to the metabolism of two long acting sulfonamides; sulfametoxipiridazine (LD_{50} for mice, applied per os 3·5 g/kg body weight) and sulfametoxipirimidine (LD_{50} for mice, applied per os, 16 g/kg body weight) with different toxicities.

420 H-strain, male mice, weighing 18–22 g were divided into groups of 5–20 animals each. The sulfonamides were applied orally in single doses of 1 g/kg body weight. At various intervals after administration of the sulfonamides (2, 4, 8 hr), the mice were killed by the sectioning of the art. carotidis, and samples of blood, liver and kidney collected for determinations. The amounts of free and bound sulfonamides was assayed by the Bratton–Marshall method.[8]

To modify the functional capacity of liver component of the RES each animal was injected with 0·2 ml of a 10 per cent colloidal India ink solution,[9, 10, 11] 48 hr before the administration of the sulfonamides, and for 5 days, previous to the administration of the sulfonamides, with daily subcutaneous 0·2 ml doses of a Reticulin solution of the peptide type.[12] The substance stimulates the functions of the reticulo-endothelial tissue, prevents and reduces the increased permeability of the capilars, determinated by histamine. The animals were subjected to a combined treatment with these substances, both to establish the concentrations of sulfonamide in the tissues, and to follow the toxicity for a period of 28 days.

The single dose of sulfametoxipiridazine (1 g/kg body weight) does not produce, over a period of 28 days, any lethality in mice (Fig. 1). In animals submitted to a previous treatment with India ink the

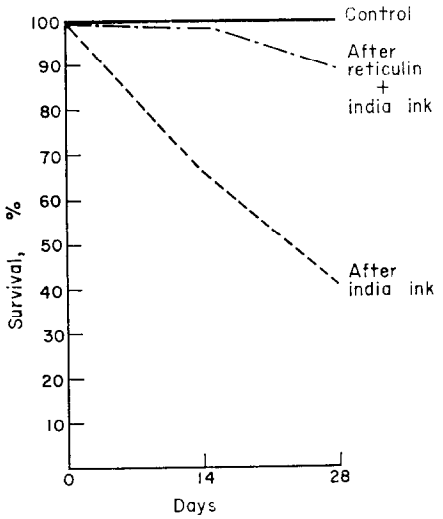

FIG. 1. Toxicity of 1g/kg per os sulfametoxipiridazine (40 animals per point).