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SHORT COMMUNICATIONS

Studies on the metabolism of sulfametoxipirimidine in endotoxin induced stress

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IN A PREVIOUS paper[1] we demonstrated that RES interferes with the metabolism of two long acting sulfonamides; the sulfametoxipirimidine metabolism being more affected than the sulfametoxipiridazine. Knowing the stress which the reticuloendothelial system (RES) undergoes in pathological processes in which the sulfametoxipirimidine is given, we studied its metabolism in endotoxin induced stress of RES.

One hundred and twenty H strain, male mice, weighing 18–22 g were divided into lots of 40 animals each group. The sulfametoxipirimidine was given orally in single doses of 100 mg/kg weight 1 hr before and 1 hr after endotoxin. To modify the functional capacity of RES each animal was injected with endotoxin *Salmonella typhi* murium (Boivin type) i.v. in LD_{50} (0·1 mg/kg).

Guinea pigs being more sensitive to endotoxin were also used. 216 male guinea pigs, weighing 250–300 g were divided into groups of 12 animals each. The endotoxin was injected i.p. in LD_{50} (0·2 mg/kg). Sulfametoxipiridine was administered as described above and in the same dose. The rectal temperature was used to control endotoxin shock at 1, 2, 3, 4, 5, 6 and 9 hr after administration. Some animals were killed by sectioning the *art. carotidis* and samples of liver collected for estimation of sulfonamide. The urine was collected from other animals during a period of 6 and 24 hr for sulfonamide estimation. The amounts of free and bound sulfonamide was assayed by the Bratton–Marshall method.[2]

In mice and guinea pigs endotoxin toxicity increased only after sulfametoxipirimidine treatment (Fig. 1). Temperature measurement in guinea pigs demonstrates the same effect: sulfametoxipyrimidine treatment increased the endotoxin induced temperature rise (Fig. 2). The amount of sulfonamide in the liver was measured after 4 hr. The tissue concentration of bound sulfametoxipirimidine was less in endotoxin treated guinea pigs (Fig. 3).

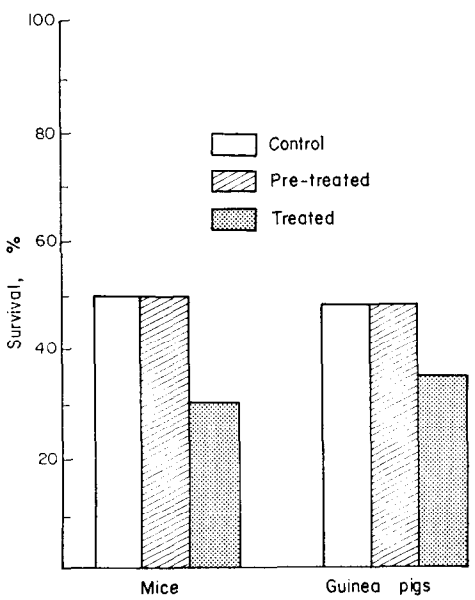

FIG. 1. Endotoxin induced toxicity in mice and guinea pigs before and after 100 mg/kg p.o. sulfametoxipirimidine (40 mice for each series, 36 guinea pigs for each series).

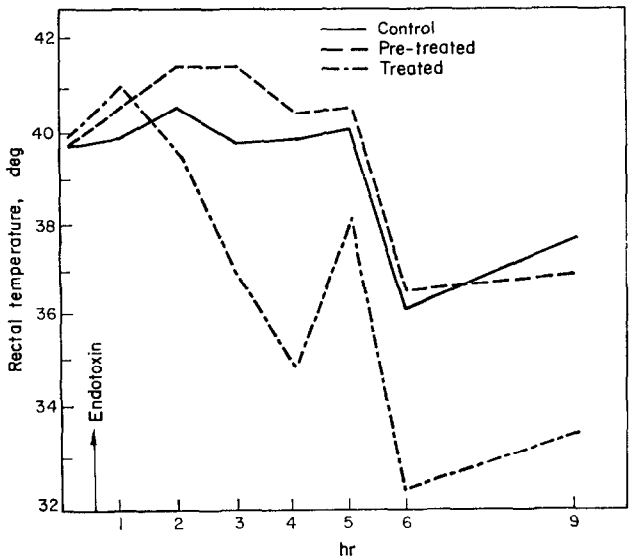

FIG. 2. Endotoxin induced thermic curve in guinea pigs after sulfametoxipirimidine (36 animals per point).

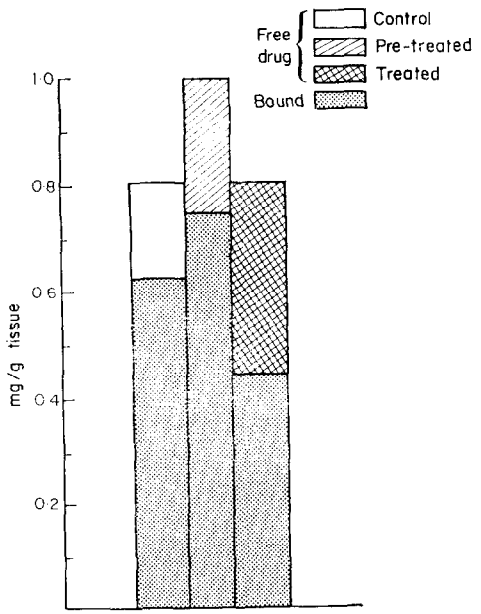

FIG. 3. Sulfametoxipirimidine level in the liver 4 hr after endotoxin administration (24 guinea pigs for each series).

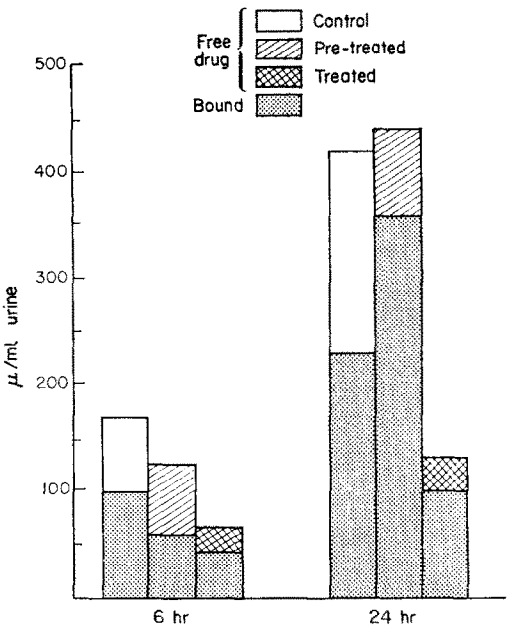

FIG. 4. Urine elimination of sulfametoxipirimidine after endotoxin in guinea pigs (36 animals for each series).

The study of urine elimination of sulfametoxipirimidine and its metabolization demonstrated that the more important modification appeared when the sulfonamide was administered after endotoxin. In this case the elimination and metabolization of the drug was almost absent.

From the findings shown in Figs. 1–4 one can see that the sulfametoxipirimidine treatment in a single dose of 100 mg/kg body wt. after endotoxin administration increased the lethality in mice and guinea pigs. The control by means of the thermic curve in guinea pigs, the liver concentration in mice and guinea pigs and the urine elimination in guinea pigs of sulfametoxipirimidine demonstrated that the increased lethality is due to its failure to be metabolized.

Our experimental findings demonstrate that the sulfametoxipirimidine is potentially toxic in endotoxin induced toxemia. This phenomenon is probably due to the blockade of its various metabolical transformations (acetylation, glucuronconjugation, etc.) and decreased urine elimination.

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REFERENCES

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