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PROPHYLACTIC ADMINISTRATION OF ANTIBIOTICS COMPROMISES RETICULOENDOTHELIAL SYSTEM FUNCTION AND EXACERBATES SHOCK MORTALITY IN RATS

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The effects of short-term (3 days) administration of three different antimicrobial agents (i.e., kanamycin, cephalothin and polymyxin B) on reticuloendothelial system (RES) phagocytic function and mortality after bowel ischaemic shock was studied in intact rats. All three antibiotics significantly depressed RES phagocytic function and exacerbated mortality after shock. The degree of antibiotic-induced inhibition of RES function seemed to parallel the antimicrobial effects on shock mortality; the greater the degree of RES inhibition, the greater the degree of exacerbation of shock mortality. In view of such findings, caution should be exercised in administering antibiotics prophylactically to patients and animals.

Introduction Controversy currently surrounds the use of systemic antibiotics for prophylaxis in surgery and trauma (Chodak & Plaut, 1977; 1979; Shapiro, Townsend, Rosner & Kass, 1979). Most clinical studies are flawed, thus preventing the acquisition of well-controlled data. Since clearance from the blood stream of pathogenic micro-organisms is dependent upon reticuloendothelial system (RES) function (Benacerraf & Miescher, 1960), it is vital to discern whether commonly used antibiotics can exert any adverse effects on this multi-potent cell system. Acquisition of such data is particularly important in relation to surgery, circulatory shock and trauma. Furthermore, it has been inferred that antibiotics can enhance survival after shock and trauma via effects on the RES (Fine, Rutenburg & Schweinberg, 1959; Palmerio & Fine, 1969). However, the exact nature of the influence of antibiotics on RES function, particularly when administered prophylactically, is not known. The available data are too scanty to be interpreted definitively.

During the past decade, evidence has been gathered which suggests that tolerance to various types of circulatory shock, trauma and surgery is associated with the functional capacity of the phagocytic cells of the RES (Altura & Hershey, 1968; 1973; Saba, 1975; Altura, 1979). Substances which depress the phagocytic powers of RE cells increase mortality, while materials which stimulate RE cell phagocytic activity, are usually associated with increased tolerance to many forms of circulatory shock, trauma and systemic stress.

In view of the importance of RE cells in host defence, and the dilemma as to whether prophylactic administration of antibiotics: (1) is judicious, and (2) influences RES function, the present study was undertaken. We have found that short-term prophylactic administration of three classes of antibiotics can depress RES phagocytic function and exacerbate shock mortality in rats.

Methods Four different groups of young adult male rats (Wistar strain, weighing 150 ± 30 g) were used. One group served as the controls and was injected twice daily for three consecutive days with isotonic sterile, pyrogen-free saline (1.0 ml/kg, intramuscularly). The other three groups were each injected twice daily for three consecutive days, intramuscularly, with a different antibiotic each, i.e., cephalothin sodium (Eli Lily and Co., 20 mg/kg), polymyxin B sulphate (Burroughs Wellcome Co., 2.5 mg/kg), or kanamycin sulphate (Bristol Laboratories, 20 mg/kg). Each sterile antibiotic was made up fresh daily and administered in a similar amount of sterile, pyrogen-free saline (i.e., 1.0 ml/kg). Phagocytic indices (or K values) were determined 18 to 24 h after the last injections, in all four groups of animals. The phagocytic indices were determined from the rate of blood clearance of colloidal carbon, 4 mg/100 g of body weight, suspended in calf-skin gelatin, as described previously (Altura & Hershey, 1968). The phagocytic indices were calculated according to the expression:

$$K = \frac{\log C_1 - \log C_2}{T_2 - T_1}$$

where C_1 and C_2 represent the blood carbon concentration at times T_1 and T_2, respectively. The means and s.e. means were calculated and statistically analyzed using Student's t test.

In other experiments, some of the saline- and antibiotic-pretreated animals were lightly anaesthetized,

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with pentobarbarbitone sodium (3.5 mg/100 g intramuscularly) and subjected to bowel ischaemic shock, 18–24 h after the last injections. The technique used here, as well as the procedure of assessing the presence of shock, was similar to that described previously (Altura & Altura, 1974). Briefly, the superior mesenteric artery was temporarily occluded for a 45 min period. After release of the arterial ligature, the wounds were sutured. The animals were then placed back in their cages, allowed food and water *ad libitum*, and observed for 7 days for survival. The statistical validity of the survival data was assessed by means of the chi-square test.

Results Short-term pretreatment of rats with three different antibiotics, in low therapeutic doses (Eichenwald & MaCracken, 1978), adversely affected RES phagocytic function (Table 1). Kanamycin prophylaxis inhibited RES phagocytic function by 38%, while pretreatment with polymyxin B and cephalothin inhibited phagocytosis by 28 and 22%, respectively. As indicated in Table 1, prophylaxis with any one of the three antibiotics resulted in significant exacerbation of mortality after bowel ischaemic shock when compared to saline controls. The degree of antibiotic-induced RES inhibition somewhat parallels the decrease in survival; or in other words, the greater the degree of RES inhibition, the greater the degree of shock mortality.

Discussion The adverse effects of short-term prophylaxis with three different antibiotics on RES function and shock mortality in rats described here support and extend some findings reported for tetracycline on fixed macrophages *in vivo* (Altura, Hershey, Ali & Thaw, 1966) and leukocytes studied *in vitro* (Martin, Warr, Cough, Yeager & Knight, 1974; Forsgren & Schmeling, 1977). This is the first report, to our knowledge, to demonstrate clearly such adverse, and potentially dangerous, effects of therapeutic, prophylactic doses of amino-glycoside (kanamycin)-, cephalosporin (cephalothin)-, and polymyxin (polymyxin B)-type antibiotics. These findings are of special interest since the former two classes of antimicrobial agents are thought to be the most generally useful drugs in the treatment of gram-negative and staphyloccal infections, and are therefore widely prescribed, both prophylactically and therapeutically.

Almost 15 years ago, we found that low doses of tetracycline antibiotic therapy in rats decreased the phagocytic activity of Kupffer cells and splenic macrophages, and in addition made these animals susceptible to another form of shock namely, whole-body trauma (Altura *et al.*, 1966). The present findings with three other classes of antimicrobial agents (in therapeutic doses) indicates that these wide-spectrum antibiotics also attenuate the phagocytic capacity of fixed RE cells and make such treated animals susceptible to bowel ischaemia shock. Previously, we suggested that the normal presence of certain pathogenic micro-organisms may play a role in maintaining RES function by stimulating various RE cells (Altura *et al.*, 1966; Altura, 1974). Collectively, the present results could be interpreted to indicate that normal baseline phagocytic function of RE cells may be under tonic stimulation of certain micro-organisms. This hypothesis will have to be rigorously tested.

Our current observations further support a role of

Table 1 Repeated administration of therapeutic doses of antibiotics produces reticuloendothelial system (RES) phagocytic depression in normal rats and exacerbates mortality after production of intestinal ischaemia shock

Antibiotic	*Dose (mg/kg)*	*RES phagocytic index (mean ± s.e. mean)*	*Intestinal ischaemia Survivors/total*	*% Survival*
Controls	Saline	0.058 ± 0.001 (92)	57/78	73
Cephalothin	20	0.045 ± 0.002** (16)	11/20	55*
Polymyxin B	2.5	0.042 ± 0.003** (18)	13/28	46*
Kanamycin	20	0.036 ± 0.002** (16)	11/31	35*

Numbers of different animals are given in parentheses.
Significantly different from untreated controls: $^{**}P < 0.001$; $^{*}P < 0.05$.

the RES in host defence and may shed light on why several antibiotics, when given to mammals, often result in supersensitivity to pathogenic micro-organisms, vascular injury and disease. In view of these findings, caution should be exercised in antibiotic prophylaxis of patients and animals.

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