

DIBEKACIN CONCENTRATION IN VARIOUS TISSUES OF PATIENTS

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Abstract

Dibekacin, 3,4-dideoxy-kanamycin B (DKB), for intramuscular injection was tested in 38 patients who were hospitalized with acute or subacute abdominal infectious diseases. They were 19 appendicitis, 8 appendicitis with perforative panperitonitis, 7 cholelithiasis with cholecystitis, 1 cholangiolitic hepatitis and 3 other diseases (gastric ulcer, left thyroid cancer and left lower leg thromboangitis obliterans). Tissue specimens of different places and plasma samples were taken during the operation from removed organs. Weight of specimens was at least over 3g.

Determination of DKB concentration was performed according to the bioassay method (bioassay with *Bacillus subtilis* ATCC 6633 strain).

In the appendicitis DKB concentrations in the appendixes were directly proportional to the degree of pathological inflammatory changes. The DKB concentrations of bile in gall bladder were higher than those in bile duct. In a gastric ulcer patient, DKB concentrations of gastric wall and appendix were trace.

INTRODUCTION

In the chemotherapy of the infectious diseases, it is very important to know minimal inhibitory concentration (MIC) of the drug for the pathogenic bacteria and affinity of the drug for the inflammatory object organ or tissues. We usually substitute the measurements of clinical blood concentration of drug for those of the object tissue itself¹⁾. The tissue concentration was directly measured from the experimental animal tissue. However, it is difficult to speculate human tissue concentration from experimental animal studies because of the pathological changes of inflammatory tissue and microcirculation of local regions.

The data measuring the concentration of antibiotics in the human infectious tissue are very few. The present study, therefore, was performed to determine the concentration of antibiotics in infectious tissues of human beings, using DKB as test sample.

MATERIAL AND METHOD

An antibiotic drug of aminoglycoside group, dibekacin (DKB) for intramuscular injection was used. The patients were 38 cases; 21 cases female and 17 male.

DKB in a dose of 100 mg was given by intramuscular injection 30 minutes before operation. Tissue specimens of different places and plasma samples were taken during the operation from removed organs. Weight of specimens was at least over 3g. The plasma samples were taken when the removed organ was clamped to stop blood flow. The removed organs were washed in saline and frozen at -20°C . The materials were preserved at -20°C for shipment. The specimens and plasma samples (kept at -20°C) were sent to the Pharmaceutical Development Laboratories, Meiji Seika Kaisha Ltd. (Kawasaki City, Japan). The tissue specimens were added 0.1M phosphate buffer solution (pH 8.0), and then were broken into pieces and homogenized. These homogenates were centrifugated at 3000 rpm for 20 minutes. Determination of DKB concentration in the supernatant was performed according to the bioassay method (Bioassay with *Bacillus subtilis* ATCC 6633 strain)²⁾.

RESULTS

The plasma concentration of DKB in a patient with gastric ulcer was $9.92\ \mu\text{g/ml}$ during the operation, when 100 mg of DKB were given intramuscularly 30 minutes before operation. But con-

centrations of gastric wall and appendix were trace.

In the appendicitis DKB concentrations in the appendixes were directly proportional to the degree of pathological inflammatory changes. DKB concentrations of plasma were 2.76~11.97 $\mu\text{g/ml}$ (mean 6.82 $\mu\text{g/ml}$). DKB concentrations of appendix in the Appendicitis catarrhalis were 0~2.95 $\mu\text{g/g}$ (7 cases, mean 2.32 $\mu\text{g/g}$), in the Appendicitis phlegmonosa they were 0~8.99 $\mu\text{g/g}$ (9 cases, mean 3.63 $\mu\text{g/g}$), in the Appendicitis gangraenosa they were 1.76~6.17 $\mu\text{g/g}$ (3 cases, mean 3.67 $\mu\text{g/g}$) and in the Appendicitis perforativa with Peritonitis purulenta they were 2.76~9.16 $\mu\text{g/g}$ (8 cases, mean 6.17 $\mu\text{g/g}$) and concentrations of purulent ascites they were 1.44~10.50 $\mu\text{g/ml}$ (mean 4.54 $\mu\text{g/ml}$).

In the patients with cholelithiasis, DKB concentrations of bile in bile duct were trace ~2.87 $\mu\text{g/ml}$, the degree of the obstructive jaundice was related to concentration of bile in bile duct⁵⁾. DKB concentrations of bile in the gall bladder were 1.15~7.19 $\mu\text{g/ml}$, and tissue concentrations of DKB in the gall bladder wall were 0~6.76 $\mu\text{g/g}$. With a few marked exceptions, DKB concentrations of bile in gall bladder were higher than those in bile duct.

It is interesting to note that in a patient of thromboangitis obliterans of left leg, DKB concentration of muscle in the amputated leg was 4.86 $\mu\text{g/g}$ and that of ischiadic nerve was 3.21 $\mu\text{g/g}$. Thus, it appears that DKB has the affinity for the nerve tissue.

DISCUSSION

Infections with gram-negative bacilli constitute a major problem, especially among hospitalized patients. Recently we obtained several drugs with broad spectrum against gram-negative bacilli. The question arises in these chemotherapy whether or not there is enough concentration of drug in the object infectious tissue after administration of the drug. However, data measuring the concentration of such medicine in the infectious tissue are very scarce^{3,4)}. Our previous study showed that in the

appendicitis doxycycline concentrations in the appendixes after intravenous administration of this drug were directly proportional to the degree of pathological inflammatory changes³⁾. In the appendix with Appendicitis catarrhalis doxycycline concentration was 1.05 $\mu\text{g/g}$ when this drug in a dose of 100 mg was administered intravenously just before operation. In the appendixes with Appendicitis phlegmonosa doxycycline concentrations were 2.20~2.88 $\mu\text{g/g}$. And in the gangraenous appendixes they were 3.26~4.25 $\mu\text{g/g}$.

Thus, these results clearly showed that antibiotics concentration of the tissue were directly proportional to degree of the pathological inflammatory changes of the tissue with infectious diseases. Similar results were also obtained when bacampicillin was administered orally (our unpublished data).

The present study, as shown with the ischiadic nerve, also indicates that DKB, a drug of aminoglycoside group, has the affinity to the nervous tissue as well as to the infectious tissues.

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