

THE LOCAL USE OF THE SULFONAMIDE DRUGS

GEORGE CRILE Jr., M.D.

Since the introduction of sulfanilamide and its derivatives, the reliance upon chemotherapy for the control of acute surgical infections has temporarily overshadowed the importance of sound surgical principles and often has resulted in the administration of inefficient or inadequate treatment. Too often, the physician fails to recognize the limitations of chemotherapy and vainly attempts to control the infection well beyond the optimum time for surgical intervention.

Chemotherapy is very effective in controlling infections from hemolytic streptococcus; is moderately effective in controlling staphylococcal infections; but is of slight value when administered systemically in patients infected with the nonhemolytic streptococcus or colon bacillus. However, even in infections caused by the hemolytic streptococcus or the staphylococcus, sulfanilamide and sulfathiazole cannot replace surgery after suppuration has taken place and mechanical drainage of an abscess is required. It is in the treatment of lymphangitis and cellulitis, not in the treatment of abscesses, that chemotherapy has been of the greatest value.

The work of Lockwood¹ and others has indicated that the products of proteolysis in vitro interfere with the bacteriostatic and bacteriocidal powers of sulfanilamide. The presence of similar substances in undrained abscess cavities probably interferes with the destruction of the organisms by chemotherapy. Accordingly, the sulfonamide drugs should supplement rather than replace early and adequate surgical drainage, especially in the presence of suppuration.

The local application of the sulfonamide drugs is based upon the principle that the local concentration of the drug in the tissues is ten to twenty times as high as that which can be obtained by any method of systemic administration. When high concentrations are reached, the drug becomes bacteriostatic for many organisms which are not affected by the oral administration of the same drug. Thus, the oral administration of sulfonamide has little or no effect upon a colon bacillus wound infection, but may reach effective concentrations in the infected tissues if the powder is sprinkled into the wound.

Since the popular acceptance of the local use of the sulfonamide drugs, a number of questions have arisen regarding the methods and the dangers of their use. The questions most frequently asked are: (1) What dangers attend the too rapid absorption and consequent overdosage of the drug? (2) Does a high concentration of the drug interfere with wound healing? (3) Are sulfathiazole or sulfapyridine more effective than the cheaper sulfanilamide in the treatment of infected wounds?

(4) Is it necessary to sterilize the drugs before applying them to clean wounds?

Question 1: Apparently there is little or no danger of overabsorption of the sulfonamide drugs when they are implanted in wounds or sprinkled upon raw surfaces. It is safe to state that the absorption of these drugs from wounds is invariably much less rapid than their absorption if equivalent amounts are given by mouth; and that much more of the drug can be safely implanted in wounds or sprinkled upon raw surfaces than can be given orally. Although 5 gms. or more of the powder has been used locally in wounds and upon raw surfaces, we have never seen the blood concentrations rise to levels higher than one-fifth of those obtained with similar amounts administered by mouth. The blood levels following local application of the drug in wounds or upon raw surfaces have not exceeded 2 mg. per cent.

When the sulfonamide drug is implanted in the peritoneal cavity, absorption may be more rapid than that following its application to wounds, but the blood levels still do not rise so fast or to levels so high as those following the oral administration of equivalent doses. It is probably dangerous to implant more than 15 gms. of sulfanilamide in the peritoneal cavity at any one time. Following implantation of sulfanilamide in the peritoneal cavity, the blood levels may rise quite high if large amounts are used; and the blood level in milligrams per cent may be expected to rise to approximately the same figure as the amount of the drug in grams which is implanted in the peritoneal cavity. Thus, if 10 gms. of the drug is implanted, a blood level of approximately 10 mg. per cent can be anticipated.

Question 2: As yet there is little evidence to indicate that the healing of clean wounds is seriously affected by the local implantation of reasonable amounts of sulfanilamide or its derivatives. If very large amounts are used, an increased serous discharge may be produced, but the prophylactic treatment of uninfected wounds requires only a light sprinkling of the powder and should not entail the implantation of large amounts. We have observed no apparent retardation in the epithelialization of clean burns following the local use of small amounts of sulfanilamide.

Question 3: Since sulfathiazole is much more effective against the staphylococcus than sulfanilamide, the local use of sulfathiazole may be preferable in the treatment of staphylococcic infections. However, as a matter of practical usage, the local concentrations of the drugs are so high that the cheaper sulfanilamide appears to be nearly as effective as the much more costly sulfathiazole. Accordingly, we prefer to use sulfanilamide locally in the prophylaxis and treatment of wound infections except in cases of stubborn staphylococcic infection. There is

THE LOCAL USE OF THE SULFONAMIDE DRUGS

never any indication for the simultaneous use of more than one of the sulfonamide drugs.

Question 4: We have not found it necessary to sterilize sulfanilamide powder before applying it to either clean or infected wounds. The powder, as it comes from the factory, is either so sterile that further sterilization is unnecessary, or its bacteriostatic powers in the tissues are so strong that any organisms are promptly destroyed. In any case, we have observed no infections in clean wounds into which sulfanilamide has been implanted, nor have we seen any reports of infections arising in clean wounds following its use.

WOUND INFECTIONS

In spite of the prophylactic, local and systemic use of the sulfonamide drugs in patients with contaminated surgical wounds, wound infections still are important and occasionally serious postoperative complications. Here again we cannot afford to rely upon chemotherapy alone, and adequate surgical drainage must be afforded in cases in which suppuration occurs. This fact was strikingly shown in a recent case of the most fulminating wound infection we have ever seen.

The patient had had a gastric resection for a very extensive carcinoma of the stomach. Twenty-four hours after the operation, the patient's temperature was 104° F. He was delirious and toxic, and examination of the wound showed a brown serous discharge and a fulminating cellulitis of the entire abdominal wall, with gangrene of the skin edges extending for an inch or more on each side of the incision. The induration, tenderness, and redness extended laterally on the left into the flank and back. Culture showed hemolytic streptococcus and colon bacillus. Sulfapyridine was given intravenously, and within twelve hours, the temperature had fallen abruptly, the patient was rational, and the spreading cellulitis was controlled. Suppuration, however, had taken place in the incision and the fascial spaces of the left flank. In spite of the local and systemic use of sulfanilamide and sulfapyridine, the incision continued to drain, the patient maintained a low grade temperature, and failed to regain his strength and appetite. Not until the subcutaneous tissues of the left flank were adequately drained by wide incision of the overlying skin did the infection finally clear up.

Before the advent of sulfanilamide, the infected area would have been treated by much earlier debridement and dependent drainage. The brilliant result from the treatment of the cellulitis made us too optimistic about clearing up the suppuration and resulted in considerable delay in the institution of adequate drainage. The limitations, as well as the assets of the sulfonamide drugs, must be recognized if such errors in judgment are to be avoided.

CARBUNCLE

A carbuncle, in its early stages, is a cellulitis from infection with the staphylococcus. Later in its development, a carbuncle suppurates to form many small abscesses. During the early cellulitis stage, a carbuncle may be amenable to treatment with sulfathiazole. Later, however, when extensive suppuration has occurred, a carbuncle rarely responds dramatically to sulfathiazole. Chemotherapy alone can only limit the further extension of the cellulitis and prevent the development of septicemia. Adequate surgical drainage or excision is still indicated, but the operation is less radical than if sulfathiazole were not used.

Roentgen therapy in the early stages of the infection also has been of value in our experience. With roentgen therapy, immobilization of the part, and application of moist heat, surgery has been avoided in nearly 50 per cent of the carbuncles so treated. After incision or excision of a carbuncle, the wound should be packed with sulfanilamide.

PHAGYDENIC ULCERS

Phagydenic ulcers are necrotizing, burrowing, subcutaneous infections, as a rule caused by streptococci and staphylococci living in symbiosis, and may respond dramatically to sulfanilamide or sulfathiazole given by mouth. More frequently, however, they react favorably to the direct application of the drug in the wound, and rarely do they fail to respond to a combination of wide debridement of all undermined skin with immediate application of large amounts of sulfanilamide in the wound. The treatment of choice before the advent of the newer chemotherapy was the application of zinc peroxide, which is now less frequently required to control these infections.

The same principle governs the treatment of phagydenic ulcer as that of any abscess. As long as pus, exudate, or the products of proteolysis are present, the sulfonamide drugs will not effectively control the infection. Wide surgical debridement is essential to remove all pockets and foci for the accumulation of pus. When these foci are eradicated, the sulfanilamide can effectively deal with the infection.

The importance of debridement is illustrated by a recent case of a huge phagydenic ulcer of the lower leg which originated in an insect bite. Although sulfanilamide and sulfathiazole had been given orally in adequate doses, the ulcer had continued to enlarge until at the end of five weeks it was six inches in diameter. A culture taken on admission showed nonhemolytic streptococci and staphylococci.

Sulfathiazole powder was sprinkled upon the wound and was packed under the overhanging skin edges. In spite of the frequent local application of large doses of sulfathiazole and the use of moist heat, the ulcer

THE LOCAL USE OF THE SULFONAMIDE DRUGS

continued to spread and the patient ran a low grade temperature. The open area of the ulcer became very clean, but the infection continued to burrow beneath the edges with the accumulation of secretions. The infection was not controlled until the overhanging flaps of skin were cut away and the wound was again sprinkled with sulfanilamide powder. Within a week, the wound was so clean that split thickness grafts were applied with a 100 per cent take.

SYSTEMIC REACTION TO INFECTION

When infections are treated with chemotherapy, the temperature frequently falls promptly to normal, and the patient appears to be cured of his infection. Despite this dramatic clinical response, the infection may, by no means, be eradicated. Too often there are residual pockets and abscesses in which, because of the presence of pus and products of proteolysis, the infection persists. Under these circumstances, the systemic reaction of the patient at first may give no clue to the presence of these abscesses. Not until after the drug is discontinued, does the patient's temperature again rise with evidences of persistent infection.

The explanation of this phenomenon is not entirely clear, although the chemotherapy may control the infection in areas of cellulitis around the abscess pockets, and accordingly reduce the absorption from these points, which was well illustrated in the case of a woman who had a diffuse staphylococcic peritonitis. With large doses of sulfathiazole, her temperature fell to normal and remained so. Even the abdominal distension subsided, and it seemed that she would recover. After her temperature had been normal for several days, she became unconscious and died, still without any elevation of temperature. Postmortem examination of the abdomen showed multiple large and small abscesses scattered throughout the entire peritoneal cavity, all of which were filled with pus. Chemotherapy had masked the signs which such an infection normally produces.

Since the sulfonamide drugs can so completely mask the systemic symptoms of residual abscesses, it is important to be constantly on the alert if abscesses are to be detected and adequately treated by surgical drainage.

CONCLUSIONS

The advent of chemotherapy has not significantly altered the surgical attitude towards suppuration and abscess. Chemotherapy alone cannot take the place of adequate surgical drainage. However, since the development of chemotherapy, the surgical approach to acute infections need not be so radical as in the past. The use of sulfonamides in the treatment of acute surgical infections does not supplant surgery, but acts as a valuable supplement to sound surgical practice.

REFERENCE

1. Lockwood, J. S.: Sulfonamide therapy as an aid to surgery, *Surg., Gynec., & Obstet.* 72:307-311 (February 15) 1941.