War Medicine Series

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SULPHONAMIDE DRUGS IN WAR

BY

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It may be emphasized at the outset that there is no essential difference between peace and war so far as the principles which govern the employment of the sulphonamide group of drugs are concerned. Nevertheless, certain infections become more prominent during wartime, and it is with these, particularly meningococcal and wound infections, that this paper deals.

Principles of their Use

The first principle is that the infecting organism must be sensitive to the drug employed, the three drugs more or less readily available being sulphanilamide, sulphapyridine, and sulphathiazole. The meningococcus is sensitive to all three drugs, but the flora of a wound may be so diverse that judicious selection may be required to get the optimum result. The following table gives a rough estimate of the sensitivity of common wound bacteria to sulphanilamide, sulphapyridine, and sulphathiazole, it being borne in mind that there may be considerable variation in the susceptibility of different strains. Thus there are strains of *Staph. aureus* which are sensitive to sulphathiazole but not to sulphapyridine, and vice versa; while most strains are to some degree sensitive to both.

	Sulphanilamide	Sulphapyridine	Sulphathiazole
<i>β</i> -haemolytic streptococcus	+++	+++	+++
<i>Staph. aureus</i>	0	++	++
<i>Proteus vulgaris</i>	++	++	++
<i>Bact. coli</i>	++	++	++
<i>Ps. pyocyanea</i>	++	++	++
<i>Str. viridans</i>	0	+	+
<i>Cl. welchii</i>	++	++	++
<i>Vibrio septique</i>	0	++	++
<i>Cl. oedematiens</i>	0	0	0

A survey of this table shows that sulphanilamide, which is cheap, readily available, and also relatively soluble, has a fair range of activity against wound bacteria, including *Cl. welchii*, the commonest gas-gangrene organism, and is therefore the drug of choice for prophylaxis in the average case, whether oral administration or local application is used, or both. On the other hand, with an established infection either sulphapyridine or sulphathiazole is indicated because of the greater range, while polyvalent gas-gangrene antitoxin should also be administered as none of these drugs has any action on *Cl. oedematiens*.

The second principle is to obtain and maintain an effective blood-stream, spinal-fluid, or local concentration, but with serious generalized infections it is essential that the administration should be four-hourly night and day: too often the night doses are omitted, with the result that the concentration during the night hours sinks below the effective level. It is an axiom that the drug must be in solution to be effective; this is of considerable importance when making local application to wounds, and rules out the insoluble sulphapyridine. For wound application a mixture of sulphanilamide and sulphathiazole gives the greatest chance of success; and in theatres of war, where most gas gangrene has been found to be due to *Vibrio septique* or *Cl. oedematiens* rather than *Cl. welchii*, sulphathiazole is certainly required. These drugs act best on small numbers of bacteria: this is perhaps the strongest argument for their free prophylactic use in wounds which from their site, extent, or nature are an open invitation to gas-gangrene infection.

A third principle involves the nature of the medium in which the drugs are called upon to act; certain substances completely inhibit action and must be excluded. Pus is one such substance, and it is therefore quite useless to expect the drugs to disperse a collection of laudable pus or to be at all effective when applied to a dirty and purulent wound; this, too, is a possible explanation of failure in deep-seated bony infections in which localizations of pus prohibit action. Nor can any great effect be expected from local application to a dirty, irregular, lacerated, pocket-laden wound, into many parts of which the dissolved drug cannot penetrate and in which foreign bodies, dirt, clothing, or bone provide an impenetrable shelter for implanted bacteria. These features show that the drugs are the handmaidens of surgery and not its master, and that the best results in wound-infection prophylaxis will be obtained by early combination of the two procedures.

A fourth general principle is to avoid prolonging treatment indefinitely when no clinical evidence of effect is forthcoming. What these drugs do they usually do quickly. Provided that adequate doses have been consistently administered at four-hourly intervals for a period of 7, or at most 10, days without beneficial action, no good can be expected from prolonging the course with that particular drug. The inference is that the infecting organism is insensitive. If further chemotherapy is contemplated the preparation should be changed: an early bacteriological examination is a useful check upon useless chemotherapy. As almost a converse to this principle it may be said that too early omission of the drug, especially in dangerous generalized infections, is apt to permit a relapse or an exacerbation; almost full doses should be continued for some 48 hours after the desired clinical effect has been produced.

Sources of Infection

The *β*-haemolytic streptococcus is introduced into a wound by human carriers and is not implanted at the time of wounding. Prophylaxis is here more a problem of hygiene than of chemotherapy. *Staph. aureus* is present in clothing and on the skin. Most other organisms are introduced by the soil. A gas-gangrene infection is implanted as spores, and the establishment of the condition is assisted by laceration of muscle, by blood clot, by the adjuvant action of aerobic bacteria, and by the presence of calcium salts. The latent period for the activation of anaerobic spores is from 5 to 12 hours, during which time, if proper surgical treatment can be given, the chance of preventing infection is good. Sometimes the infection is fulminating and is well established within a few hours. It is obvious that gas-gangrene infections will be most frequent in mobile warfare when there is unavoidable delay in obtaining surgical treatment.

Wound-infection Prophylaxis

The object of prophylactic chemotherapy is, first, to prolong the latent period before infection has become established until such time as proper surgical treatment can be obtained, and, secondly, to ensure that any residual infection after débridement shall be eliminated. If the two procedures can be combined so much the better. Oral administration is feasible in the most advanced positions in a battle zone; local application is neither so easy nor so likely to be efficient, because the wound has been neither cleaned nor trimmed. Nevertheless, the general opinion is that local application at the earliest possible moment is desirable even though efficient surgery has to be delayed: at least partial inhibition may be accomplished, and if supplies are adequate the procedure is justifiable. A second application at the time of débridement should always be made. Animal experiments have shown that local application alone does not prevent invasion of the blood stream by the *β*-haemolytic streptococcus; oral administration is also required in order to obtain a sufficiently high blood-stream concentration. On the other hand, local application, properly applied, is more effective in preventing the establishment of anaerobic infection than is oral administration; the anaerobes, too, are far less invasive than the *β*-haemolytic streptococcus, and the relatively low blood-stream concentration which local application engenders is high enough to prevent this complication. The general conclusion from animal experiment is that local application combined with small doses by mouth is necessary for efficient wound-infection prophylaxis. No exten-

sive systematic assessment has yet been made, but the clinical impression of those who have seen active service is that these measures are effective and certainly superior to the use of antiseptics such as eusol, acriflavine, and hydrogen peroxide.

Dosage in Wound-infection Prophylaxis

For local application sulphanilamide is the drug of choice unless sulphathiazole is available, in which case a mixture of two parts of the former and one of the latter should be employed. From 5 to 15 g., according to the size of the wound, should be applied as a fine powder. However numerous the wounds not more than 15 g. should be used. The application should be made as early as possible and be repeated at the time of débridement. It is necessary to keep the wound moist with a saline gauze dressing or to cover the powdered wound with a vaseline spread. This last is recommended by Mitchell, Logie, and Handley (1941), who have had extensive experience in the Middle East. These same authorities recommend 5% sulphanilamide in 80% glycerin for deep cavities and joints. The powder may be applied with an insufflator, a pepper-pot, or even a tablespoon; it should be distributed evenly and completely, if this is possible, or applied to a moist saline gauze and thrust deep into the wound when circumstances demand. A War Office Memorandum (1940) recommends for oral administration an initial dose of 1.5 g. sulphanilamide followed by 0.5 g. four-hourly for 3 or 4 days as uncrushed tablets. The sooner this is administered the better, but it is important that all doses, and the time, should be recorded on the label attached to the patient, in the same way as morphine and antitetanic serum are recorded. Mitchell, Logie, and Handley (1941) consider these doses far too small for severe cases, and recommend as much as 4 g. for an initial dose, with subsequent four-hourly doses of 1.5 g. for 4 to 6 days, night and day; they state that they have seen many die from too little sulphanilamide but none from too much. To those who have the boggy of agranulocytosis always before them these heroic doses may appear to invite disaster; there is no doubt they are the upper limit, whereas the War Office Memorandum doses are definitely cautious. There is considerable scope for clinical judgment between the two limits according to the nature of the wounds, the higher doses being used when indications suggest that gas gangrene is inevitable. Similarly, clinical judgment will sometimes suggest that an early administration of gas-gangrene antitoxin is justifiable.

Treatment of Established Wound Infection

With acute infections both oral and local treatment should be undertaken. On account of their greater range either sulphapyridine or sulphathiazole should be used for the oral doses. Oral dosage may be as much as 10 to 12 g. daily for 7 to 10 days with a severe and extensive gas-gangrene infection; antitoxin in doses of 20 to 40 c.cm. daily for 4 or 5 days is also advisable. Frankly purulent wounds need to be cleaned up before local application is made. Chronic wound infection does not demand oral therapy unless a generalized infection appears likely; all purulent material must be removed from the wound before local application is made. Excellent results have been obtained, with rapid healing, in wounds resulting from burns. Skin-grafting may be practised on a wound-bed previously sprinkled with sulphanilamide.

Meningococcal Infections

With early administration and adequate dosage bacteriostasis is complete within 12 to 24 hours. In epidemics early recognition of cases is of first importance. With unconscious patients a soluble preparation is required at the outset, but this should give place to an oral one as soon as swallowing is re-established. The soluble preparation should never be administered intrathecally, and most authorities do not advocate the giving of serum. Sulphapyridine and sulphathiazole are somewhat more effective than sulphanilamide, and sulphathiazole is preferred on account of its less nauseating reaction. A normal fluid intake should be arranged. For adults the "loading dose" is 2 to 3 g. and the maintenance dose 1½ g. four-hourly night and day for 2 to 3 days; thereafter 1 g. four-hourly for 2 days, followed by 0.5 g. four-hourly for 2 to 3 days; total dosage 40 to 50 g., according to clinical judgment. Failure to respond to this schedule of dosage usually means that the concentration

in the cerebrospinal fluid has not reached the required amount of 3 to 5 mg. per 100 c.cm. When samples of spinal fluid are sent for estimation of drug content care should be taken that no traces of novocain are present in the sample, as this anaesthetic gives a colour reaction similar to that of the sulphanilamide group. Meningococcal septicaemia responds to somewhat smaller doses; the amount recommended is a loading dose of 2 g. followed by 1 g. four-hourly until 48 hours after the temperature has become normal. The meningococcal carrier has always been a problem. Modern opinion is that a bacteriological search for carriers is not worth while in view of the ease with which the infection itself can now be controlled. There is as yet no proper estimate of the value of sulphathiazole snuff in the treatment of obvious carriers; it is claimed, however, that 1 g. of sulphanilamide by mouth six-hourly for 6 days entirely clears the carrier state.

Bacillary Dysentery

Intestinal infections are a major problem, in Eastern theatres of war. For the treatment of bacillary dysentery sulphaguanidine, when available, has proved of great value. This drug has the curious property of being soluble in the intestinal contents but of being poorly absorbed unless there is a grossly ulcerated surface. The dosage employed is large, amounting to as much as 20 g. a day for 5 or 6 days.

REFERENCE

Mitchell, G. A. G., Logie, N. J., and Handley, R. S. (1941). *Lancet*, 1, 713.

INJURY TO LIMBS

A ROEHAMPTON CONFERENCE

At the invitation of the Director-General of Medical Services of the Ministry of Pensions, a conference of surgeons was held at Queen Mary's Hospital, Roehampton, last September, Mr. G. R. GIRDLESTONE presiding.

Ward Demonstration

Mr. T. P. KILNER and Mr. GEORGE PERKINS opened with a demonstration of plastic and orthopaedic cases in the wards. Mr. Kilner urged that "the best dressing for a large open wound is skin," and suggested that all surgeons in charge of accident services should be given the special equipment which facilitates the cutting of large Thiersch grafts of selected thickness. He gave a most useful demonstration of cases illustrating the use of thick Thiersch, tubular, and flap grafts. Mr. Perkins first showed a patient with the moderate but disabling degree of equinovarus associated with the relative weakness of the external popliteal group of muscles after a partial sciatic recovery. These patients are much benefited by an inside iron, outside T-strap, and a toe-raising spring attached to the outer side of the sole opposite, but not distal to, the fifth metatarsal head. He then illustrated by a number of patients his belief that it is the use, as natural as possible, of the muscles surrounding the fracture which stimulates and accelerates union. He limits the extent of his plaster splints to the margin of safety, and dislikes the Böhler iron and the single stick. He likes a heel-and-toe movement, with particular attention to the active use of the toes. Crutches or two sticks with less splintage are preferred to a long plaster which makes full weight-bearing safe. He goes so far as to recommend that splintage can often be discarded, at least during the waking hours, on palpable evidence and before radiographic evidence of union.

Deranged Knee-joint

Prof. R. J. WILLAN opened a discussion on "failures following operation for derangement of the knee-joint." He stressed the value of an exact history, and the far greater value of the evidence which can be elicited by x-ray examination as well as by clinical examination. Once again it was made clear that the diagnosis of an internal derangement, indicating the removal of a semilunar cartilage, requires great care and much consideration. Furthermore, if this is true in civil life, a decision to operate on a soldier or a pensioner requires even greater and more deliberate judgment. Mistakes