REFRESHER COURSE FOR GENERAL PRACTITIONERS

SULPHONAMIDE THERAPY

BY

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The pre-eminent place of sulphonamides in the treatment of many infections has been usurped by penicillin. Their prerogatives indeed are likely to be curtailed still further when the newer antibiotics come into more general use. Nevertheless, they still have a wide application in therapeutics: they are the drugs of choice in meningococcal meningitis, since penicillin passes the blood-brain barrier uncertainly and with difficulty, and in dysenteric and coliform infections, which are unaffected by penicillin; they are almost as effective as penicillin in pneumococcal pneumonia and erysipelas, in which their use is preferable because of their relative cheapness and the convenience of their oral administration; they have been superseded by penicillin in gonococcal and staphylococcal infections and to some extent in streptococcal infections, particularly in septicaemias, except in those cases in which the organism has proved to be penicillin-resistant. When a purulent complication has occurred sulphonamides are ineffective.

The evidence favouring the employment of sulphonamides to prevent the respiratory complications of measles, common colds, and influenza, and for the prophylaxis of the complications of scarlet fever, is in my opinion insufficient to justify their routine use for such purposes. There is considerable statistical evidence that their prophylactic use in daily doses of 0.5 g. for long periods is of value in preventing the recurrences of acute rheumatism, even though sulphonamides are useless in the treatment of the established condition. There seems to be little danger in giving such small doses even for years; nevertheless, further controlled studies must be undertaken before this form of treatment can be recommended in general practice.

Experience gained in the recent war seems to indicate that the use of crystalline sulphonamides and of sulphonamide ointments as topical agents is not very successful in the treatment of infected wounds or in infections of the skin and mucous membranes. Moreover, the prolonged use of sulphonamide creams and ointments often results in severe and intractable forms of sensitization dermatitis. The routine use of sulphonamides as topical agents is therefore to be discouraged, except in the form of eye-drops for the treatment of conjunctivitis, corneal ulcers, and blepharitis, and to prevent infection after injuries to the eye. Even here a mild chronic blepharitis may result from the use of sulphacetamide.

In summary, then, the main indications for sulphonamide therapy to-day are in the treatment of meningococcal, coliform, and dysenteric infections; lobar pneumonia; erysipelas; certain infections of the eye; and in infections due to haemolytic streptococci, gonococci, and staphylococci when these have proved resistant to penicillin.

Absorption, Fate, and Action

When sulphonamides are swallowed they are absorbed to a greater or less extent from the small intestine. Some preparations are completely absorbed, others are hardly absorbed at all. When they are absorbed they become

rapidly distributed among all the body fluids, though their concentration in milk is too low to affect a suckling baby. The amino-nitrogen in these compounds is partly acetylated in the body—the degree of acetylation varying according to the preparation used. The acetylated form has no therapeutic effect. A mixture of the free drug and acetyl compound is excreted in high concentration in the urine, but about 30% of the sulphonamide is destroyed in the body.

The concentrations of sulphonamides in the blood (5 to 15 mg. per 100 ml.) which are obtained by therapeutic doses do not kill organisms but inhibit their growth so that they are dealt with by the ordinary defence mechanisms. Their action is due to their inhibiting effect on the metabolism of *p*-aminobenzoic acid, which is required by many species of organism as a growth factor.

Preparations and Choice of Drug

There are numerous official preparations of sulphonamides, many of which are marketed by manufacturers under an astounding variety of names, one of the few undesirable expressions of the inventive genius of the great pharmaceutical firms. The practitioner may well be bewildered by the number of preparations at his disposal and doubtful about which drug to use in any given circumstance and how to use it to the best advantage. Many of the sulphonamides differ only very slightly from one another, and it is more important to know how to use a few properly than to be continually changing to an unfamiliar preparation because of some slight advantage it may be reputed to possess. Actually only three or at most four preparations need be employed; one or possibly two for general infections; one for intestinal infections; and one for application to the eye.

The following are brief notes on the main attributes of the more important sulphonamides.

Sulphanilamide (B.P.) is the active principle of the original sulphamidochrysoidin ("prontosil red") introduced by Domagk in 1935. It is rapidly and completely absorbed and quickly excreted. It is relatively soluble so that it does not produce renal complications, though in other respects it is more toxic than the newer sulphonamides and less therapeutically active, having no effect on pneumococcal infections. Its prescription is now seldom indicated.

Sulphapyridine—the famous "M. and B. 693"—has been omitted from the 1948 *British Pharmacopoeia* because of the severe toxic effects it produces, particularly nausea and vomiting. There is nothing it can do that modern sulphonamides cannot do better, and it should never be prescribed nowadays.

Sulphathiazole (B.P.) and *Sulphadiazine* (B.P.) closely resemble each other. They are both highly active and are rapidly absorbed and excreted, so that they have to be given at short intervals in high dosage to maintain adequate blood concentrations. Both drugs and their acetyl derivatives are relatively insoluble in acid urine. Sulphadiazine is rather less toxic than sulphathiazole, and of the two is probably the preferable drug.

Sulphadimidine ("sulphamezathine") and *Sulphamerazine* (U.S.P.) have almost identical qualities. I am prejudiced in favour of the former—possibly on account of its British origins.

Sulphadimidine is more rapidly and completely absorbed than sulphadiazine, so that with equal oral doses sulphadimidine attains a blood concentration approximately twice that of sulphadiazine. It is also more slowly excreted, so that it may be given in smaller amounts and less frequently. The acetylated and free forms of sulphadimidine are more soluble than sulphadiazine in neutral and acid urine, and are thus much less apt to give rise to renal complications, though in other respects the two drugs have approximately the same degree of toxicity. Thus, sulphadimidine is probably the best sulphonamide for routine use, though, as it is possibly a little less active than sulphadiazine, the latter may remain the preferable drug in severe meningococcal meningitis.

Sulphadiazine and sulphadimidine are insufficiently soluble for parenteral administration except in the form of their *sodium salts*. Such solutions are strongly alkaline and should be administered only intravenously. Ampoules containing 1 g. of dry powder are available, and the contents should be dissolved in 10 ml. of normal saline. An excellent alternative is "soluthiazole," which is supplied in rubber-capped bottles ready for use; 5 ml. are equivalent to 1 g. of sulphathiazole. It is a neutral solution and so can be given intramuscularly as well as intravenously—a considerable advantage where babies are concerned. It is seldom necessary to give the drugs parenterally except in very severe infections when it is desirable to obtain rapidly a high concentration of sulphonamide in the blood, or when the patient is comatose and unable to swallow, or when intense vomiting prevents absorption.

Sulphatriad, a combination of sulphathiazole, sulphadiazine, and sulphamerazine, is recommended on the principle that if two or more sulphonamides are administered in combination the therapeutic actions of the different compounds are additive but their solubilities remain independent of each other. Accordingly, it is possible to obtain a high blood concentration without the risk of renal complications. Since we have in sulphadimidine a powerful and relatively soluble sulphonamide it seems superfluous to use sulphatriad, which is also more costly.

Sulphacetamide (B.P.) yields a very soluble and almost neutral sodium salt (sulphacetamide sodium B.P.) which can be used as eye-drops in concentrations up to 30%.

Sulphaguanidine (B.P.), *Succinylsulphathiazole* (B.P.), and *Phthalylsulphathiazole*, though soluble in the intestinal contents, are all relatively poorly absorbed, thus permitting them to exert their bacteriostatic action in the intestinal tract. Hence their only use is for intestinal infections, particularly dysenteric infections, and for treatment before and after operations on the colon. All three are non-toxic, but succinylsulphathiazole and phthalylsulphathiazole are absorbed even less than sulphaguanidine and are therefore preferable to it. There is some slight evidence that succinylsulphathiazole is superior to phthalylsulphathiazole in acute dysentery and for the elimination of the carrier state.

From what has been said it would seem that the following four sulphonamides are probably the drugs of choice: sulphadimidine for lobar pneumonia, erysipelas, and coliform infections; sulphadiazine and its sodium salt for meningococcal meningitis; succinylsulphathiazole for intestinal infections; and sodium sulphacetamide for infections of the eye.

Administration and Dosage

Sulphonamides are marketed in tablet form, each of which contains 0.5 g. ($7\frac{1}{2}$ gr.). The tablets should be broken into small fragments and swallowed with 2–3 oz. (57–85 ml.) of milk or water. The drugs should be given in full dosage or not at all. The only exception to this rule is in infections of the urinary tract (see below). Full dosage should be maintained till the treatment is stopped. The administration of sulphonamides should seldom be continued for longer than seven days and never for more than ten days. It is always advisable to give an initial "loading dose." Children tolerate the drugs well and require a larger dose than might be expected on a purely weight basis. Over the age of 12 they can be given the full adult dose; between 3 and 12, two-thirds of it; between 1 and 3, one-third; and under 1, one-sixth.

In *lobar pneumonia* and *erysipelas* a "loading dose" of 3 g. of sulphadimidine should be given, followed by 1 g. six-hourly till the temperature has been normal for two or three days.

In *coliform urinary infections*, owing to the fact that sulphonamides are concentrated by the kidneys in their passage from the blood into the urine, it is unnecessary to give the large doses required in other diseases. A "loading dose" of 2 g. of sulphadimidine should be given, followed by 0.5 g. six-hourly.

In *meningococcal infections*, in view of their serious nature, the "loading dose" of sulphonamide should be given intravenously in the form of at least 1 g. of sodium sulphadiazine. The injection should be made slowly. Thereafter 2 g. of sulphadiazine should be given orally followed by 1.5 g. every four hours. Treatment should be terminated only when the cerebrospinal fluid has been sterile for some days and all physical signs are in abeyance. This usually involves the administration of sulphadiazine for seven or eight days. As dehydration is common in cerebrospinal fever, and as there is a real danger of renal complications when sulphadiazine is used under such circumstances, every effort must be made to maintain an adequate fluid intake, if necessary by the use of parenteral fluids. As sulphadiazine is much more soluble in an alkaline medium an attempt must be made to render the urine alkaline by the administration of a mixture containing 20 gr. (1.3 g.) each of potassium citrate and sodium bicarbonate—the frequency of dosage being determined by the reaction of the urine to litmus.

In *acute bacillary dysentery* succinylsulphathiazole can be given in massive doses with complete safety, since little is absorbed into the blood. At least 3 g. should be given four times a day and continued for some days after the stools have become normal. Prolonged treatment, which is perfectly safe with this drug, may be necessary in the eradication of the convalescent and chronic carrier state. The drug has been recommended in idiopathic ulcerative colitis, but in my experience is of little or no value.

In *infections and injuries of the eyes* sulphacetamide sodium is used as eye-drops, though penicillin is more effective in severe infections such as ophthalmia neonatorum. In the treatment of acute conjunctivitis and in the prophylaxis of ocular infections after injuries a few drops of a 10% solution are instilled every two hours. An ointment containing 5% of the drug may be smeared along the roots of the lashes three times a day in the treatment of blepharitis.

Toxic Effects

When modern sulphonamides are properly used toxic effects should be rare, and virtually confined to those few

patients who have become sensitized to the drugs or who have an idiosyncrasy to them.

Some malaise and loss of appetite are not uncommon as the result of sulphonamide therapy, but the distressing vomiting so common after the use of sulphapyridine is seldom produced by the more modern drugs.

A harmless cyanosis due to methaemoglobin was often encountered during treatment with sulphanilamide but is rarely occasioned by the drugs which have been recommended. Very exceptionally, sulphaemoglobinaemia develops, accompanied by cyanosis, shallow respirations, and a rapid pulse of poor quality. I have seen this complication on only one occasion. A slow recovery usually occurs when the drug is withdrawn. Sulphaemoglobinaemia is probably due to absorption of sulphides from the large bowel, and, as this is facilitated by fluid colonic contents, the use of saline purges is inadvisable in conjunction with sulphonamide therapy.

Sensitization phenomena, taking the form of a drug fever with or without a skin rash—usually a widespread rose-red maculo-papular rash which fades on pressure—may occur in a previously sensitized individual after a single dose of sulphonamide or may appear from the fifth day of treatment onwards. In the latter case, when there is only a fever and no rash, it may be difficult to distinguish this toxic manifestation from a recrudescence of the disease. When these sensitization phenomena occur or are suspected it is wise to stop sulphonamide therapy and to change to penicillin or one of the other antibiotics if further treatment is indicated. Sensitization to sulphonamides is common and serious enough to render it highly undesirable to resort to sulphonamide treatment for every minor infection which may occur in practice.

Owing to the low solubility of sulphadiazine and especially of its acetyl derivative the risk of microscopic or gross haematuria and ultimately anuria may be considerable following its use under conditions which reduce the output of urine, such as an inadequate fluid intake, vomiting, diarrhoea, or excessive sweating. These renal complications may be prevented by ensuring a fluid intake of at least five pints (2.8 litres) and preferably six pints (3.4 litres) a day, sufficient to maintain a urinary output of not less than 50 oz. (1.4 litres), and by rendering the urine alkaline. The occurrence of a microscopic haematuria is a warning signal to institute prompt preventive measures. Provided the urinary output is normal the discovery of crystals of the drug in urine which has stood for some time is of no significance. The development of anuria calls for immediate cessation of sulphonamide therapy and for forcing oral and parenteral fluids. If this is not rapidly successful specialist aid should be sought and a trial made of ureteric catheterization. Sulphadimidine practically never gives rise to these renal complications.

Blood dyscrasias are rare after sulphonamide treatment unless it is prolonged beyond ten days, or unless previous sensitization phenomena have been disregarded. They include purpura, haemolytic anaemia, aplastic anaemia, and agranulocytosis. The occurrence of these disorders is an absolute indication to stop treatment.

A few cases of peripheral neuritis have been reported following sulphonamide therapy.

The Nursing Appointments Service of the Ministry of Labour and National Service has been reorganized. One result is that there will be 135 offices of the Ministry instead of 33 where nurses and midwives and would-be nurses and midwives can receive advice about these careers and any help they may want in obtaining posts.

INTERNATIONAL CONGRESS OF RADIOLOGY MEETING IN LONDON

The Sixth International Congress of Radiology, attended by 2,700 members from 54 countries, was opened by the EARL OF ATHLONE, chancellor of the University of London, on July 24 at the Central Hall, Westminster. Dr. RALSTON PATERSON was invested with the insignia of office as president of the Congress, and gave an address in which he pictured the evolution of radiology from its troglodytic days in beetle-infested basements to its modern status as a mature science helping medicine in diagnosis and treatment. On the evening of the same day British Radiology gave a dinner at the Guildhall to over 600 guests from many countries. The Lord Mayor of London and Vice-Admiral Earl Mountbatten of Burma were the guests of honour, and the latter, in proposing the toast of Radiology, referred to the advanced course in radiological defence and atomic medicine given to civilians and members of the Services at the Royal Naval Medical School at Alverstoke.

The scientific meetings took place in three main groups: (1) General Congress Symposia, four in number; (2) a series of symposia in each of the four main subdivisions of radiology—radiodiagnosis, radiotherapy, radiobiology, and radio-physics; (3) meetings of all four sections, with the addition of electrolgy, at which more than 300 papers were delivered.

General Congress Symposia

A symposium on supervoltage radiotherapy was held on July 25 at which Dr. R. S. STONE (U.S.A.) evaluated the late effects of the use of radiation in excess of 1,000 kV. There were definite advantages, although the relatively high incidence of deep fibrosis of tissues counselled caution. Dr. O. DAHL (Norway) described the 1,500 kV generator at Bergen, and discussed the factors influencing the choice of voltage and the engineering problems involved. Professor B. W. WINDEYER, the chairman, pointed out that, in the range of one to four million volts, therapy has now emerged from the technically experimental stage and is available for clinical evaluation. Advantages to be derived and problems of organization were discussed.

On the following day Sir STANFORD CADE (London) opened a symposium on radiological achievements (1937–50) with a review of the clinical aspects of radiodiagnosis and radiotherapy, and marked the recent milestones of progress. Dr. EDITH QUIMBY (U.S.A.) pointed out the need for a unified and adequate system of dosimetry for high energy radiations now being developed. She described some instruments designed to meet special problems in this field. Dr. A. LACASSAGNE (France) dealt with the advances in the understanding of the actions of radiation on living tissues, in the physio-chemical mechanism of direct and indirect radiation, and with some aspects of cytoplasmic changes in the cell. Dr. ROSS GOLDING (U.S.A.) reviewed advances in gastro-intestinal radiology, with particular emphasis on the radiology of the small intestine and the use of the Miller-Abbott tube. Gall-bladder radiology had been improved by the introduction of a new opaque medium. Dr. P. FARINAS (Cuba) also discussed opaque media, while Dr. K. LINDBLOM (Sweden) considered the use of water-soluble iodine compounds in the study of trauma to joint-cartilages and other structures. Dr. J. LAWRENCE (U.S.A.) outlined the present status of treatment with radioisotopes of iodine and phosphorus. Dr. RALSTON PATERSON (Manchester) dealt with advances in clinical radiotherapy (1937–50).

Mass radiology of the chest was discussed on July 27. Professor M. DE ABREU (Brazil) traced the development of his work from the earliest attempt at fluorography in 1923 to the final methods presented in 1936. Problems relating to the efficient employment of 180 units operating in Brazil were discussed. He gave some details of the chest diagnostic service which works alongside the mass survey for the further assessment of abnormal shadows. He touched upon the social implications of mass radiology. Dr. A. C. CHRISTIE (U.S.A.), who is ill and whose paper was read by Dr. Orndoff, outlined the development of mass radiology in U.S.A.; it was first applied on a large scale to the examination of the U.S.