EMERGENCIES IN GENERAL PRACTICE

DANGEROUS REACTIONS TO SULPHONAMIDES AND ANTIBIOTICS

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The introduction of the sulphonamides and, more recently, the antibiotics into clinical practice is now recognized as one of the most startling advances made by man in his attack on disease. Serious reactions to both groups of substances are comparatively uncommon and even more rarely result in permanent damage. To write an article which is solely concerned with such reactions and which omits reference to the benefits that may be obtained from the administration of these therapeutic agents gives the former undue importance. None the less, because such reactions do occur, it seems proper from time to time to repeat the statement that the indiscriminate use of either sulphonamides or antibiotics can produce harmful results and that their administration always carries a risk, however small this may be.

The comparative rarity of severe reactions implies that any individual lacks wide personal experience of them, and considerable reliance has to be placed on reported cases and figures from the literature. Insufficient details in such reports are all too often provided while statistics are often confined to selected groups of cases. It is difficult from such sources to obtain a clear idea of the incidence of reactions. None the less, this information is of the greatest significance to the practising doctor, and, although a good deal of literature has been reviewed in arriving at the figures quoted in this article, these cannot be regarded as being very accurate. Particular use has been made of the review carried out by Kutscher, Lane, and Segall,* which seems to be the most complete attempt to find this information.

In general, the reactions produced by sulphonamides and antibiotics can be grouped under the following headings: (1) general allergic and anaphylactic reactions; (2) reactions affecting the gastro-intestinal tract; (3) reactions affecting the kidney; (4) reactions affecting the nervous system; and (5) blood dyscrasias.

General Allergic and Anaphylactic Reactions

Such responses may be produced by either group of substances. They range from angioneurotic oedema and asthma to the sudden onset of weakness, sweating, collapse, and death. In their most severe form death occurs usually within twenty minutes after the injection of the substance or within one to two hours after oral administration. The most severe reactions usually follow parenteral administration.

Penicillin, which is perhaps the most widely used, has produced the greatest frequency of severe reactions of this type and probably the greatest number of deaths. The incidence of severe reactions is probably of the order of 3% of patients treated, and it would appear that penicillin has a higher haptogenic potency than most of the other antibiotics or sulphonamides. There is some evidence that such reactions are becoming increasingly common; only two deaths were recorded in the first nine years after the introduction of penicillin, and 15 within the next two years. Reactions are most common when penicillin is given by injection, but they have followed its oral use, its topical application, and its instillation into the pleura and peritoneum. They occur most often in patients with a family or past history of allergic phenomena and there can be no doubt that penicillin should be used cautiously in such patients. Even in these patients severe reactions are rare on first exposure to the antibiotic; in patients without such a history severe reactions are hardly recorded during the first occasion on which penicillin has been used.

Dispute has arisen as to whether the long-acting penicillin preparations now widely used produce a higher incidence of severe and fatal reactions, and at the present time evidence on this point is lacking. Recent alarming case reports of severe reactions with long-acting penicillins have called attention to the possibility, and it has been suggested that a substance which is slowly absorbed from an injection site would produce more profound reactions because absorption continues after the sensitivity response has started. The fact that this does not occur in experimentally produced allergy and our ignorance of the exact mechanism and nature of allergic responses to penicillin make it quite possible that the suggestion is unreal. Different penicillins themselves vary in their haptogenic potency, while both procaine and benzathine, used to delay absorption, have such potency in their own right. If reactions are more severe or occur more often with long-acting preparations, the most probable reason is that both substances—penicillin and procaine or benzathine—may act independently in this way.

General reactions are probably less common with streptomycin, which produces a higher incidence of severe skin lesions, and are rarely associated with the use of other antibiotics or sulphonamides. They have, however, been recorded with almost all the commonly used preparations.

The severity of allergic reactions varies greatly. Although death may occur within a few seconds of their onset, prompt treatment has proved life-saving in many instances. The basis of emergency treatment is the administration of adrenaline hydrochloride. A syringe is charged with 1 ml. of a 1 in 1,000 solution and 0.1 ml. injected subcutaneously. The syringe should be left *in situ*, as further injection may be necessary if there is little relief or if there is recurrence of symptoms following the disappearance of the transient action of the adrenaline. Administration can be continued until 1 ml. has been given, unless the pulse rate rises steeply. Less acute reactions may be treated by the intermittent injection of adrenaline or the administration of ephedrine orally, ¾ gr. (50 mg.) three times a day. Chronic reactions —mainly those of urticarial type—can be treated by the administration of antihistamines such as mepyramine maleate, 50–100 mg. thrice daily, and promethazine hydrochloride, 25 mg., at night.

Gastro-intestinal Reactions

Effects on the gastro-intestinal tract have been recorded with all the antibiotics and the sulphonamides. In the mouth, erythematous and raw areas may appear, secondary infection with *Candida albicans* or other organisms may take place, and a gangrenous condition ensue. This chain of events occurs particularly in elderly debilitated patients and in those whose oral hygiene is unsatisfactory. It occurs most often, but not exclusively, with chlortetracycline, oxytetracycline, and chloramphenicol. The incidence is probably about 3% of patients treated. There can

*Kutscher, A. H., Lane, S. L., and Segall, R., *J. Allergy*, 1954, 25, 135.

be little doubt that if this condition complicates an existing illness it can be severe enough to add to the mortality; certainly it is most distressing to the patients. The incidence of such conditions is much lower with sulphonamides (less than 0.1%), but oral penicillin preparations give a high rate of occurrence. At the other end of the gastro-intestinal tract, pruritus ani and looseness of the stools associated with proctocolitis occur, and can add seriously to the discomfort and illness of elderly patients. They may also persist long after the drug has been withdrawn.

More serious, however, is the diarrhoea which is due largely to small intestinal infection with resistant organisms, particularly *Staphylococcus aureus*. Deaths occur in the young and in the elderly. In one series of patients with measles treated with chlortetracycline, or chloramphenicol, or penicillin and streptomycin combined, 22 patients out of 195 developed diarrhoea and 14 of these died. There seems little direct correlation between the length of treatment and the onset of diarrhoea except that it occurs after several days' treatment. Once it has started, however, death may take place with alarming rapidity. Of the 14 deaths recorded above, 11 patients died within 24 hours of the onset of diarrhoea. The incidence of the condition seems to be highest with chlortetracycline and oxytetracycline, somewhat lower with streptomycin, while with penicillin and the sulphonamides it is comparatively rare. The figures range approximately from 2 to 8% with the first group down to insignificant proportions with the sulphonamides. Very severe disturbance probably occurs in 10 to 15% of those affected.

One other reaction which is common but rarely severe is nausea and vomiting. Orally administered antibiotics and many of the sulphonamides produce these symptoms, and haematemesis has been recorded as a result of the vomiting. Although liver damage has occasionally been reported in the literature it seems probable that the main effects of the antibiotics and sulphonamides on liver function are, on the whole, beneficial.

In patients with acute diarrhoea the administration of the causative antibiotic should be stopped immediately. Death is usually due to acute dehydration, and intravenous fluid therapy should be started as soon as possible. These patients usually require between 8 and 11 litres of fluid in the first 24 hours, a third to a half of it being in the form of normal saline. In more chronic conditions, particularly those associated with moniliasis, whether of the mouth, bowel, or ano-rectal region, encouraging results have been reported from the use of "nystatin" ("mycostatin"). This is an antibiotic obtained from *Streptomyces noursei* which is given orally in doses of half to one million units. It can be applied topically. It is probably of little value in general infections as it is not absorbed from the bowel. It has been suggested that this substance might be given concurrently with the administration of wide-spectrum antibiotics to prevent the occurrence of such infections. The more usual treatment is to attend to the local hygiene and try to encourage the return of the normal bowel bacteria. Yoghourt, "marmite," and "bemax" have given good results in some cases. Symptomatically, chlorpromazine will assist in the treatment of persistent vomiting.

Renal Hazards

The tendency for crystalluria, renal calculi, and anuria to occur after the administration of sulphonamides is well known. Sulphapyridine, sulphathiazole, and sulphaguanidine have produced the highest incidence of such reactions. The danger of these complications can largely be offset by using a combination of three sulphonamides, but even with this precaution these conditions still occur. Deaths have been recorded as a direct result of them, and in other cases they have undoubtedly contributed to the mortality. Impairment of renal function without gross crystalluria or frank calculus formation has also been recorded, although permanent renal damage seems comparatively rare. With most of the sulphonamides used alone, the incidence of crystalluria or renal calculi appears in the neighbourhood of about 5 to 15%, while complete anuria occurs in about 10% of those affected. Patients particularly liable to these complications are those who are dehydrated either because of profuse sweating or vomiting or because they are unable to take large quantities of fluid by mouth. Prolonged rest in bed may also facilitate the occurrence of renal calculi.

Less well documented are the renal complications associated with antibiotic therapy. Albuminuria, impaired renal function, and lower nephron nephrosis have all been recorded in association with the administration of most of the antibiotics. Bacitracin, neomycin, streptomycin, and polymyxin B seem to give the highest incidence. In the case of neomycin, renal damage often seems to become permanent. Polymyxin B has perhaps the most evil reputation in this respect, but in the early days of its administration much of the damage may have been due to the presence of a related substance in the preparations, polymyxin D. The reports concerning later preparations have been less alarming. The incidence of such reactions with these four substances is probably in the neighbourhood of 5 to 20%, being highest with bacitracin and less common with neomycin and recent preparations of polymyxin B. Chlortetracycline and oxytetracycline give a fairly high incidence of transient albuminuria, but there are few recorded cases of impaired renal function or permanent renal damage. Penicillin seems to be singularly free of complications in this respect. Kutscher and his colleagues could not find a single example of renal damage attributable to penicillin in a review of the literature covering systematic records of 18,519 patients receiving the drug.

Treatment of these renal conditions is largely prophylactic. The maintenance of a high urinary output and the careful selection of the sulphonamide to be used are of the greatest importance. The administration of alkalis has been recommended, but their value is probably not very great. Even when there is marked oliguria, increase of the fluid intake is usually sufficient to alleviate the condition. Surgical measures such as ureteric irrigation may be necessary.

Neurotoxic Effects

The most striking neurotoxic effects of the sulphonamides and antibiotics are those produced by streptomycin and dihydrostreptomycin on the eighth nerve. Streptomycin appears to affect mainly vestibular function, while dihydrostreptomycin affects mainly the auditory division of the nerve. These changes are startling; firstly, because of their frequency, which probably amounts to about 20% of the patients given these drugs; serious permanent damage probably occurs in about 8% of the total or just under half of those getting symptoms. Secondly, the symptoms may develop some weeks after the administration of the antibiotic has stopped, for where careful follow-up studies have been done a higher incidence of these complications is recorded. The symptoms are giddiness, tinnitus, and deafness. They occur most commonly in elderly patients in whom the incidence must be higher than the figures given above. Accentuation of similar symptoms already existing in the elderly is extremely common and many of these patients who were previously able to live without major disability from their giddiness have been turned into invalids after the administration of streptomycin. Of the other antibiotics, polymyxin B seems to have a similar effect, and in addition transient ataxia commonly occurs. Sulphapyridine and sulphadiazine have probably given the highest incidence among the sulphonamides, while chlortetracycline, oxytetracycline, chloramphenicol, and penicillin give almost no trouble in this respect.

Although the commonest, disorders of eighth nerve function are by no means the only neurotoxic effect of these drugs. Peripheral neuritis has been associated with the

administration of penicillin, streptomycin, and the sulphonamides, its incidence probably being well below 1% of patients treated. The elderly seem to be particularly susceptible.

Mental disturbances occur with all these drugs, but their relationship to the antibiotic or sulphonamide is difficult to assess; the recorded figures probably depending upon how thoroughly such changes are sought. The transient intense depression, particularly in patients with cyclothymic personalities, which occurs during the administration of the sulphonamides, especially with sulphapyridine, is a common experience. It probably occurs in some degree in 10 to 15% of all patients to whom this substance is administered. It is slightly less common with chlortetracycline and polymyxin B. The onset of frank psychosis associated with the administration of these drugs is rare but it has in fact been recorded in respect of almost all commonly used preparations. Transient toxic confusional states with mental irritation, dizziness, nervousness, disorientation, and insomnia occur quite often and on rare occasions may reach serious proportions. In these cases it is always difficult to distinguish the effect of the sulphonamide or antibiotic from that of the disease for which it has been given. Less well documented are the number of elderly patients who get permanent disturbances of sensation and behaviour after having had a course of these substances. Once again, it is almost impossible to dissociate the effect of the disease from the effect of the treatment, but it is clear that more work on this problem needs to be done in view of the known neurotoxic effects of both the sulphonamides and the antibiotics. The administration of the vitamin-B complex may do something to minimize these neurotoxic effects, but its value is still doubtful.

Blood Dyscrasias

Leucopenia and agranulocytosis are among the commonest complications of sulphonamide and antibiotic therapy. They occur most often during the administration of sulphonamides, in severe form probably having an incidence of about 1% of patients receiving these drugs. Sulphadiazine and sulphapyridine appear to give the greatest incidence. Leucopenia and agranulocytosis have also been reported with streptomycin, chloramphenicol, and chlortetracycline, to a less degree, while penicillin seems to be singularly free from this complication. In the acute form the onset is sudden and dramatic, the granulocytes disappearing within a few days and the throat becoming severely infected. The onset may occur at any time during administration of the drug, but is most common during the first three weeks.

If agranulocytosis develops the antibiotic should be immediately withdrawn. The inability of these patients to resist infections, particularly with streptococci, is the most frequent cause of death, and the basis of treatment is the administration of penicillin. The agranulocytosis lasts for a minimum of seven to nine days, and penicillin treatment must be continued for at least this time. If the blood count still shows absence of granulocytes treatment should be continued. Certain substances have been reported to stimulate the production of white cells in the bone marrow, and, indeed, it seems that all have some action. It is probably best, therefore, in this serious condition to administer them all at once. They are pyridoxine hydrochloride, 50 mg. three times a day, folic acid, 20 mg. a day, both given orally, and nucleotide injection (*B.P.C.*), 40 ml. a day, intramuscularly.

In its milder and more chronic form the granulocyte count diminishes gradually and the administration of the sulphonamide or antibiotic has to be stopped.

Anaemia may arise in several different ways. Depression of bone-marrow function, sometimes associated with leucopenia, is perhaps the commonest. It occurs in association with sulphonamide therapy, particularly with sulphapyridine, sulphathiazole, and succinylsulphathiazole, and with the administration of chloramphenicol. Treatment with the other antibiotics seems relatively free of this complication. Anaemia may also occur as a result of a haemolytic process; most of the recorded cases have been associated with the administration of sulphonamides. This form may be acute in onset and fatalities have been recorded. Finally, it may arise as a result of bleeding from the gastro-intestinal tract associated with diarrhoea, proctocolitis, or gastric haemorrhage. Usually this last form of anaemia occurs during the administration of chlortetracycline, chloramphenicol, or oxytetracycline.

Where bone-marrow aplasia is the cause of anaemia, transfusion of fresh whole blood is the best treatment. The haemoglobin should be raised to about 90% (each pint (0.6 litre) raises it by about 8%) at a rate of not more than 1 pint (0.6 litre) every eight hours. Where chronic haemorrhage is the cause, less extensive transfusion is required, the aim being to raise the haemoglobin above a safety level of about 60%; further transfusion may increase the rate of haemorrhage. Transfusion in this instance should be combined with the administration of iron, which is probably best given either as ferrous sulphate, 18 gr. (1.2 g.) a day, orally, or in the form of sterile saccharated iron oxide solution—for example, "iviron" or "ferrivenin"—intravenously. The dose of the intravenous iron is 100 mg. of elemental iron daily for 10 days if the haemoglobin is 60% or below.

Thrombocytopenia is a rare complication of sulphonamide therapy, but cases have been reported with all the commonly used sulphonamides. The same mechanism operates as in acute haemolytic anaemia, the sulphonamide providing an antigen which produces platelet lysis in sensitized subjects.

Conclusion

It is realized that this review is incomplete. Such large and important questions as the general problem of increasing resistance of organisms to antibiotics, superinfections, and rare complications have been omitted. On rare occasions, for example, both polyarteritis nodosa and diffuse lupus erythematosus have been ascribed to the use of antibiotics and sulphonamides; in these cases, however, it is difficult to be sure of the causal relationship, though the evidence is suggestive. The prognosis is so bad in patients with these conditions that the possibility cannot be ignored.

Finally, it is necessary to stress again the bias of such an article as this. These few complications are small in importance compared with the beneficial effects that the sulphonamides and antibiotics have brought. Almost every form of therapy involves taking a calculated risk, and the complications with these drugs merely make it mandatory that the indications for their use must be carefully considered in every patient and that they should never be used if less noxious remedies or no therapy at all would be as effective.

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