Drug Treatment of Disease

DRUG TREATMENT OF TUBERCULOSIS

I. STANDARD CHEMOTHERAPY

BY

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The aims of the drug treatment of tuberculosis are to arrest the patient's disease, to render him uninfectious, and to prevent relapse. In patients with pulmonary tuberculosis whose organisms are initially sensitive to the standard drugs it should be possible to achieve these aims in all, or virtually all, patients provided the drugs are carefully prescribed and carefully taken. Error on the part of either doctor or patient can lead to the emergence of drug-resistant organisms. The patient with such organisms may be extremely difficult to salvage. In few other conditions can apparently minor error lead to such ultimate disaster for the patient.

Standard Drugs

The three standard drugs in the treatment of tuberculosis are streptomycin, isoniazid, and the salts of para-aminosalicylic acid (P.A.S.). A number of other drugs are now available, but none of them has yet found a place in the routine treatment of patients. They are at present reserved for those whose organisms are resistant to the standard drugs.

Toxic Effects of the Standard Drugs

Streptomycin

Streptomycin is available as the sulphate or as the calcium chloride complex. The drug is given by intramuscular injection, and the sulphate is the least painful salt. The two main toxic effects are *vestibular upset*, resulting in giddiness, and hypersensitivity reactions. Vestibular upset, if it occurs at all, usually does so within the first three months of administration; the liability to giddiness does not seem to increase with prolonged administration beyond this period. Vestibular damage appears to be more common in older people. Even a relatively slight renal insufficiency is liable to result in the retention of streptomycin, with consequent risk of vestibular damage. If there is any likelihood of renal impairment, it is wise to investigate the serum levels of streptomycin.

Our standard practice is to give 1 g. streptomycin intramuscularly and to estimate the serum level 24 hours later. If the level is greater than 1 μg. per ml., there is retention of streptomycin, and the dose should be lowered accordingly. If giddiness does occur streptomycin should be immediately stopped. It is normally possible to continue chemotherapy with P.A.S. and isoniazid. If streptomycin is stopped as soon as giddiness begins, recovery is usual, but if the drug is continued after the vestibular damage has occurred recovery may take many months, especially in older people.

Deafness due to streptomycin is extremely rare if the drug is given in normal doses by the intramuscular route. It may occur after intrathecal streptomycin. A modification of streptomycin, dihydrostreptomycin, was introduced in an endeavour to reduce the incidence of vestibular damage. Vestibular damage is certainly less common with dihydrostreptomycin but unfortunately this drug may cause deafness even when given by the intramuscular route. It should never be given intrathecally.

It has been suggested that the incidence both of vestibular damage and of deafness may be reduced by using a mixture of dihydrostreptomycin and streptomycin, but the incidence of auditory damage seems to be sufficient for this combination not to be recommended for routine use.

Hypersensitivity reactions are relatively frequent with streptomycin. They usually come on within the first four weeks of treatment and are manifested by fever or rash or both. Occasionally there may be enlargement of the lymph glands as well. Any fever occurring within the first month of treatment should be regarded as due to drug hypersensitivity until proved otherwise. The drug should be immediately stopped until the reaction has subsided. P.A.S. and isoniazid will have been stopped at the same time, for hypersensitivity may be due to P.A.S. also.

A test dose of streptomycin is then given. If the reaction has not been a severe one, it is reasonable to give a dose of 0.5 g. If the reaction has been severe then it is wise to start with a smaller dose, perhaps 0.1 g. If the patient is hypersensitive, a rash or some rise in temperature usually occurs within a few hours. If there is no response a larger dose can be given. If there is no reaction to a full dose the patient is not hypersensitive to streptomycin.

If hypersensitivity is proved, it is usually adequate to start desensitization with a dose of 0.1 g., though lower initial doses may have to be given to some patients who have had very severe reactions. The dose can normally be increased at the rate of 0.1 g. daily. If there is any reaction it is well to repeat the previous dose after the reaction has subsided and then to work the dose up slowly again. Desensitization is normally possible within two to three weeks. In occasional patients who are very hypersensitive, desensitization may have to be carried out under cover of corticosteroid drugs.

Isoniazid

In the doses recommended below for treatment of all tuberculosis except tuberculous meningitis, isoniazid only very rarely indeed gives rise to any side-effects. The most common side-effect is peripheral neuritis, usually manifested by a burning sensation in the limbs. Psychotic upsets have also been described. When very large doses of isoniazid are given, such side-effects are a definite hazard, and their incidence is said to be greatly reduced by giving prophylactic pyridoxine at the same time as the isoniazid. A daily dose of 60 mg. seems to be adequate for this purpose. Hypersensitivity reactions to isoniazid are very rare and usually occur in patients who are also sensitive to streptomycin and P.A.S. Desensitization can proceed on similar principles.

P.A.S.

In Great Britain P.A.S. is normally given orally. The most important side-effects are *nausea* and *diarrhoea*. Nausea is relatively common when the higher doses, such as 20 g. of the sodium salt daily, are given, but is very much less usual when P.A.S. is given in a daily dose of 10 g. It often helps to take the dose in the middle of a meal. In severe cases it may be justifiable to reduce the dose somewhat and then work it up gradually. Several preparations are on the market which are alleged to improve the tolerability of P.A.S., but some of these are not well absorbed from the gut. We have found two preparations—"bactylan," and P.A.S. and isoniazid tablets (Carnegie)—to improve tolerance and to be well absorbed.

Diarrhoea is less common but may be very troublesome. It is usually not prevented by using enteric-coated preparations. If small doses of tinct. opii are given, this will often allow the bowel to become accustomed to the drug, and the tinct. opii can be withdrawn after quite a short time. Very occasionally a patient is quite unable to tolerate P.A.S.

Hypersensitivity reactions are common and their manifestations are similar to those of streptomycin, though jaundice and even encephalitis have been described in severe cases. The principles of desensitization are also similar. If the reaction has been mild a test dose of 2.5 g. is adequate, but with a more severe reaction a lower test dose, such as 0.5 g. or even 0.1 g., may be necessary. When desensitizing in the ordinary case, an initial dose of 0.5 g. is usually small enough, though after a very severe reaction the initial dose sometimes has to be very much smaller. In the usual case a daily increment of 0.5 g. is adequate, and desensitization is completed in two to three weeks.

Simultaneous hypersensitivity to streptomycin and P.A.S. is not uncommon, and tests should always be carried out to both drugs. It is probably best to begin by desensitizing to P.A.S., to which resistance is less readily acquired, and to add in isoniazid when the patient is able to tolerate half the normal daily dose of P.A.S. When the full dose of P.A.S. has been reached P.A.S. and isoniazid can be continued while desensitization to streptomycin is proceeding.

P.A.S. has a weak *anti-thyroid* action. Some patients who have been on it for six months or more may develop a goitre or even hypothyroidism. Either can be relieved, while continuing the P.A.S., by administering thyroid. Thyroid function returns to normal when the patient ceases to take P.A.S.

Drug-Resistance

Tubercle bacilli readily acquire resistance to all three of the standard drugs. A proportion of naturally resistant mutants occurs in any large population of bacilli. Under the influence of a single drug the resistant bacilli gradually increase until the sensitive population are replaced by the descendants of the resistant mutants. Fortunately by giving proper doses and combinations of drugs the emergence of resistant tubercle bacilli can be avoided in all, or almost all, cases. The mutants naturally resistant to one drug are eliminated by the other. If the patient's tubercle bacilli have become drug-resistant, they usually remain so permanently. With single drug therapy in a patient with a large population of tubercle bacilli, resistant organisms may occur as early as two or three weeks after starting treatment, though more commonly in four to eight weeks.

When a patient's bacilli becomes resistant to a drug, then that drug ceases to be effective. In particular, if given in combination with a second drug, it fails to prevent the emergence of bacilli resistant to the second drug. The criteria for drug resistance vary considerably in different centres. Experience in this department has shown that the lowest detectable degree of drug resistance may be clinically significant.

Unfortunately a patient who develops drug-resistant organisms may pass these on to others, and a previously untreated patient may present with organisms which already are resistant. Surveys have shown that between 5 and 7% of newly diagnosed patients have organisms "primarily" resistant to one or more of the standard drugs. Fortunately only a very small proportion of patients have organisms primarily resistant to two standard drugs.

If proper chemotherapeutic combinations are widely used, resistant organisms should not develop and should not be diffused in the community. The incidence of primary drug-resistance should therefore diminish. But at the present time, in certain parts of the world at least, the incidence is probably rising.

Recommended Drug Combinations

The following drug combinations are based on carefully controlled comparative studies of the Medical Research Council. Most have been used for seven to eight years by the Edinburgh group, with, in pulmonary tuberculosis, almost uniform success in converting the sputum to negative, provided the organisms were initially sensitive to at least two of the standard drugs.

(1) Hospital Patients Under Age 40

Streptomycin 1 g. daily intramuscularly +sodium P.A.S. 5 g. three times daily +isoniazid 100 mg. twice daily.

All three drugs are given initially in case the patient has been infected with organisms resistant to one of the drugs. The remaining two drugs would then form an effective combination in preventing resistance. The dose of 100 mg. isoniazid twice daily was used in the Medical Research Council trial but is lower than the dose used in very many parts of the world. It has been found that many patients metabolize isoniazid rapidly, and it has been suggested that the dose of the drug should be based on serum estimations. But at least in British conditions this seems unnecessary, for even with our lower dose several series have been published showing uniform conversion of the sputum to negative and without the emergence of resistant bacilli.

(2) Hospital Patients Over Age 40

Streptomycin 1 g. three times weekly +sodium P.A.S. 5 g. three times daily +isoniazid 100 mg. twice a day.

The lower dose of streptomycin in this group is given because of the risk of vestibular disturbance in older people. Theoretically there might be a slight risk of drug resistance with this combination, for if the patient's organisms were primarily resistant either to P.A.S. or to isoniazid he would virtually be receiving intermittent streptomycin with daily doses of the other drug. In practice we have not seen a failure of this type, but it

remains a theoretical possibility. Perhaps it might be safer to give a daily dose of 0.5 g. streptomycin, but we have at present no evidence that this would be superior.

In the case of hospital patients under the age of 40, once it is known that the pre-treatment cultures were sensitive to all three drugs the P.A.S. may be stopped. The combination of daily streptomycin and isoniazid has been shown in the Medical Research Council trials to be the most efficacious. In patients over the age of 40 we cannot stop the P.A.S., as it is risky to give intermittent streptomycin with daily isoniazid: some patients may develop isoniazid-resistant organisms.

(3) Mild Cases Treated as Out-patients and Patients After Discharge from Hospital

It is convenient to treat the patients in these categories with oral drugs. The usual combination is 5 g. sodium P.A.S. together with 100 mg. isoniazid, both twice daily. Isoniazid and P.A.S. are given in the same cachets or the same tablets, so that the patient cannot take one without the other.

In newly diagnosed patients with mild disease there is the theoretical objection that some of these patients may have been infected with organisms resistant to one of the drugs, with the risk of the development of resistance to the second. It might be safer to administer all three drugs, at least until it is known that the pre-treatment cultures are sensitive or negative. But there may be an even larger hazard if the patient is given his streptomycin injections and fails to take his P.A.S. and isoniazid. It is possibly therefore a lesser risk to prescribe P.A.S. and isoniazid from the beginning of treatment and to keep streptomycin in reserve.

Risky Chemotherapy

Certain drug combinations and commercial preparations of drugs, though they may be successful in the majority of cases, may give rise to a much higher failure rate than the standard drug combinations mentioned above. The Medical Research Council trials showed that streptomycin given twice a week with daily isoniazid resulted in isoniazid-resistant organisms in up to 13% of patients within six months. When streptomycin was given daily with P.A.S., a daily dosage of 5 or 10 g. P.A.S. was greatly inferior, in preventing streptomycin resistance, to a daily dose of 20 g. Our experience has suggested that intermittent streptomycin with daily P.A.S. also carries a risk of the emergence of drug resistance.

Several preparations are on the market which consist of chemical combinations between P.A.S. and isoniazid, mixtures of isoniazid with thiosemicarbazones or other drugs, or allegedly better tolerated forms of P.A.S. It is probable that most of these preparations are less effective than the standard combinations. It is unwise to use any of them until they have been tested out in a really critical and scientific manner. The unsupported assurances of advertising material should not be accepted.

Duration of Chemotherapy

Studies of the relation of relapse rate to duration of chemotherapy, and also studies of the isolation of tubercle bacilli from lung lesions resected after varying periods of chemotherapy, suggest that one year should be the minimum period of chemotherapy in any form of tuberculosis, however mild. In moderately severe cases chemotherapy should be continued for eighteen months; in very severe cases, including those with residual open cavities, for two years. There is little present evidence that a duration of more than two years is necessary. Among 260 cases of pulmonary tuberculosis admitted to Edinburgh hospitals with sensitive organisms in 1953 and 1954, and receiving a minimum of eighteen months' chemotherapy, there were no relapses within three to five years.

Corticosteroid Drugs

It has been established that corticosteroid drugs given in severe pulmonary tuberculosis increase the rate of subjective improvement, weight gain, and radiological clearing, at least during the early months of treatment. Nevertheless, at least when prednisolone in a daily dosage of 20 mg. was given for three months, the ultimate results in the patients who received corticosteroids were not significantly better than in the controls.

It is of course highly dangerous to give corticosteroid drugs if the patient's organisms may not be sensitive to the chemotherapy in use. There seems little point in using corticosteroid drugs as a routine. The risks are not balanced by any ultimate benefit to the patient. But corticosteroids may keep alive a patient who is admitted moribund until the antituberculous drugs can take effect. In patients who are very toxic, corticosteroid drugs may be given in the earlier weeks, largely for humanitarian reasons. As already mentioned, they also have a place in the treatment of patients with severe hypersensitivity reactions in whom desensitization may prove difficult.

Failure of Out-patients to Take Drugs as Prescribed

When it became possible to test for P.A.S. in the urine it soon became obvious that many out-patients failed to take their drugs as prescribed. The physician must be tireless in persuading the patient to take his drugs regularly. It is important that the possible disasters which may result should be explained not only to the patient but also to his near relatives. For, even when P.A.S. and isoniazid are made up in the same cachet, if the patient fails to take the appropriate number of cachets during the day his bacilli can become isoniazid-resistant.

For patients judged to be unreliable it may be possible to arrange a daily injection of streptomycin, with simultaneous administration of the full daily dose of isoniazid under the nurse's supervision.

Chemotherapy of Non-Pulmonary Tuberculosis

The principles of the chemotherapy of non-pulmonary tuberculosis are very similar to those already outlined. In the case of tuberculous meningitis many clinicians give a daily dose of isoniazid of 10 mg. per kg. body weight in two or more divided doses. It is uncertain whether intrathecal streptomycin is necessary. In any case a daily intrathecal dose should not exceed 100 mg. streptomycin and in young children 50 mg.

Intrathecal isoniazid has been advocated and is possibly justified in very severe cases. The intrathecal dose should not exceed 40 to 50 mg. daily for an adult and correspondingly smaller doses for children. Pure isoniazid powder must be used and the solution sterilized by filtration.

Tuberculosis of the urogenital tract responds excellently to chemotherapy, and arrest of the disease

should be as well assured as in pulmonary tuberculosis. However, healing may give rise to scarring and stenosis and this in turn may lead to mechanical difficulties. In all cases of renal tuberculosis, streptomycin levels in the serum should be estimated early in treatment in case there is retention of the drug. In all severe forms of extrapulmonary tuberculosis it is wise to continue chemotherapy for at least eighteen months.

Conclusions

Provided proper sensitivity tests have shown that the patient's organisms are sensitive to the standard drugs and that chemotherapy is scrupulously prescribed and scrupulously taken, it should be possible to arrest the disease permanently in the vast majority of cases. There may be very occasional failures in patients admitted moribund, in cases of severe tuberculous meningitis, or in miliary tuberculosis in young infants. But any carelessness by the doctor in prescribing, or by the patient in taking, his drugs are liable to result in ultimate drug resistance and often in subsequent disaster for the patient. Unfortunately such carelessness is still all too common. Treatment of its results will be discussed in the next article in this series.

ADDER-BITES IN CORNWALL

BY

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In the last eight years I have seen 12 cases of adder-bites in adults and children and have been consulted about another six. In 14 years in the Middle and Far East I have treated only two cases of snake-bite in Europeans. What is the reason for this anomaly?

During the holiday season, from mid-June until mid-September, Cornwall is faced with an influx of visitors, mainly from the industrial north. The majority are town-bred people, complete strangers to our countryside, in holiday mood, and intensely curious and interested in their unfamiliar environment of tent, caravan, or bed-and-breakfast with its compulsory accompaniment of alfresco meals by lane, wood, or beach.

This period coincides with the breeding season of *Vipera berus*, our only venomous snake. Nearly all the bites I have been consulted about have occurred on the fingers or arms due to foolish attempts to capture or handle the vipers.

The Criminal

The adder (*Vipera berus*) is not an aggressive snake, it strikes only in self-defence when handled or trodden on; where the human race is concerned it is never the aggressor. It is a short stumpy snake; the largest recorded British specimen was 2 ft. 3 in. (68.5 cm.) in length—this was a female; the male is 2 to 3 in. (5 to 7.5 cm.) shorter. It is usually possible to distinguish the sexes by the coloration: whitish or pale-grey specimens with a black belly and jet-black dorsal markings are males; brown and brick-red specimens with the markings of a darker brown or red are females. The markings vary considerably; those on the back usually consist of a wavy or zigzag longitudinal band; rarely, the markings may be absent altogether and occasional black melanistic specimens occur (Boulenger, 1913).

Vipera berus is the only poisonous snake in Great Britain; it is absent in Ireland. As in all vipers, the two poison fangs are hollow and are present in the posterior extremity of the erectile maxilla; the venom from the poison gland (a modified salivary gland) is injected into its prey to immobilize it and facilitate swallowing and also digestion. The venom of *Vipera berus* is not very toxic; the minimum lethal dose (M.L.D.) for a 600-g. guinea-pig is 40 mg., as compared with the M.L.D. of a Russell viper which is 1 mg. for a similar-sized guinea-pig. The venom contains a small amount of neurotoxin, which varies considerably in the different species of the same genus. Haemorrhagins are also present. The haemorrhagin has a special affinity for the endothelial cells of the finer capillaries, causing lysis of the cells and subsequent haemorrhagic oedema or small petechiae. The latter may be present at the site of the bite and may spread up the affected limb. Oozing of blood from the site of the bite occurred in only one of our Cornish cases; no sloughing of tissues occurred, so the cytotoxins present in the venom, although responsible for the oedema and swelling, are not very toxic.

Feeding Habits

The food of the adder is very varied; baby rabbits, weasels, mice, voles, shrews, moles, birds, lizards, slow-worms, frogs, and large slugs have been found in the stomach. It swallows its prey whole, the neurotoxin paralysing it and the cytotoxins and haemorrhagins injected deeply into the victim facilitating digestion.

Hibernation occurs during the colder months of the year, but bites have been recorded from March until October.

I am convinced that the varying severity of adder-bites in this country is dependent on whether the snake has bitten anything recently. This is well exemplified in the case of a boy aged 11, who was bitten on the left index finger and then on the right index finger. No haemorrhagic bullae developed on the right index finger, and the purpuric petechiae and swelling of the right hand and arm were much less. Similarly, the only adult male whose condition gave rise to anxiety was bitten in the early spring by a hibernating viper.

Reproduction

Pairing takes place in April and May, and the young, 5 to 20 in number, are born in August and September. The young, on releasing themselves from the transparent membrane in which they are enclosed at birth, measure 6 to 8 in. (15 to 20 cm.) in length and feed on insects and worms.

Natural Enemies

Owing to the dearth of rabbits since the onset of myxomatosis the buzzards in Cornwall have been seen killing adders by flying upwards with the adder in their talons and dropping it from a height of about 150 ft. (46 m.). The water bailiff at the reservoir assures me that he has seen this on at least three occasions. The stunned snake is then torn to pieces and eaten by the buzzard.