Topics in Therapeutics

Edited by P. Turner

Topics in Therapeutics 2

Edited by Paul Turner, M.D.

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Editor's Foreword

The second Topics in Therapeutics conference was overshadowed by the recent death of Professor Gordon Hamilton Fairley, since, before what Sir Ronald Bodley Scott described as "the senseless outrage" occurred, Gordon had been due to speak on the treatment of Hodgkin's disease. The paper presented at short notice by Dr T J McElwain was a worthy tribute to his work.

I would like to express my thanks to Sir Ronald Bodley Scott, Sir Eric Scowen and Professors J Marshall, F W O'Grady and M Shepherd who were chairmen and gave invaluable advice on the organisation of the different sessions, and to the speakers who agreed so readily to participate.

I am also most grateful to my secretary Miss Jill Walker and to Miss Sally Freeman, Conference Secretary of the Royal College of Physicians, for their help in all the many details of preparation of the Conference. This book would not have appeared without the persistent enthusiasm and expert help of Mrs Betty Dickens of Pitman Medical Publishing, whom I thank most sincerely.

Paul Turner

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Contents

The Treatment of Imported Infections

A M GEDDES

Most of the infections which are imported into the United Kingdom originate in tropical or sub-tropical countries. During the past 25 years there has been a great increase in air travel for holiday and business purposes and, with the increased range and speed of modern aircraft, it is now possible to fly to Northern Europe from most areas in the world within 24 hours. Travellers quite frequently arrive in the United Kingdom incubating infections which are not normally endemic in this country. Immigration from the Indian sub-continent and the Caribbean has further contributed to the increase in the incidence of imported infections.

Certain tropical diseases, notably the protozoal infections, respond extremely well to chemotherapy but others, e.g. helminth infections, are more refractory. For virus diseases such as smallpox and rabies there is as yet no specific treatment. Recently, problems of drug resistance have emerged, examples being chloramphenicol-resistance of the typhoid bacillus, chloroquine-resistant falciparum malaria and dapsone-resistant leprosy.

This paper is not a comprehensive review of the treatment of all tropical diseases but merely a comment on experience with imported infections in one large hospital in England. Only the commonor imported infections will be discussed and general outlines of treatment described. For more detailed information and descriptions of rarer diseases a standard textbook of Tropical Diseases should be consulted.

The treatment of imported infections will be discussed under the following headings:

1 Protozoal infections
2 Bacterial and rickettsial infections
3 Helminth infections
4 Virus infections

Protozoal Infections

The two most important protozoal infections encountered in the United Kingdom are malaria and amoebiasis.

During the past five years there has been a very significant increase in notifications of malaria in the United Kingdom. Falciparum malaria can be rapidly fatal and requires urgent treatment, especially in non-immune subjects.

Infections caused by *Entamoeba histolytica* have an insidious onset and, as a result, diagnosis can be difficult and is frequently delayed. Amoebic disease of the large bowel may be confused with ulcerative colitis and thus treated with corticosteroid drugs with potentially serious consequences.

Infections caused by the other important protozoal organism *Glardia lamblia* are commonly contracted by travellers to both tropical and temperate countries and can cause persistent and troublesome gastrointestinal symptoms.

Trypanosomiasis is rarely encountered in Europe but leishmaniasis is endemic in eleven European countries (Lancet, 1975), particularly around the Mediterranean littoral.

Malaria

Quinine first became available for the treatment of malaria in 1820. It is a very effective anti-malarial compound but relatively common side-effects, including tinnitus and the precipitation of blackwater fever, led to a search for less toxic drugs. The 4-aminoquinolones, notably chloroquine which interferes with the digestion of haemoglobin by plasmodia, were introduced in 1944 and subsequently almost replaced quinine as the drug of first choice for the treatment of malaria.

Chloroquine is generally free from serious untoward effects but is neurotoxic and can cause fatal encephalopathy if given by rapid intravenous injection to young children. Rapid intravenous injection in adults can cause peripheral circulatory failure. Very rarely, oral chloroquine can produce neurotoxic side-effects. It has an anti-inflammatory action similar to that of salicylates and thus relieves the acute symptoms of malaria as well as killing the parasites. Chloroquine is active against all forms of malaria and is usually administered in an initial dose of 4 chloroquine phosphate tablets, each containing 150 mg of chloroquine base, followed six hours later by 2 tablets and then 2 tablets daily for a further two days. For parenteral administration to vomiting or seriously ill patients the dose is 200-300 mg, although children must not be given more than 5 mg per kg body weight by intramuscular injection.

Chloroquine will effect a complete cure in malaria caused by chloroquine-sensitive *Plasmodium falciparum* strains but will not eradicate the extra-erythrocytic forms of *Plasmodium vivax* from the liver in benign tertian (BT) malaria. To prevent a recurrence of BT malaria it is necessary to follow chloroquine therapy with a 14 day course of the 8-aminoquinoline compound, primaquine. The dose for adults is 15 mg daily but for infections contracted in South-East Asia 30 mg daily may be required to effect a cure. This drug can cause haemo-

lysis, particularly in patients suffering from glucose 6-phosphate dehydrogenase (G 6-PD) deficiency and should only be given under medical supervision.

Malignant tertian (MT) malaria caused by chloroquine-resistant *P.falciparum* strains has recently become a problem in Asia east of Burma and also in South America. A number of regimes have been suggested for the treatment of MT malaria caused by chloroquine-resistant plasmodia. Quinine is usually recommended for this purpose. In seriously ill patients it should be given by intravenous *infusion* over a period of 2-4 hours in a dose of 10-20 mg per kg body weight per 24 hours (Hall, 1975). A total of 4 doses should be given at 8 or 12 hourly intervals. The plasma level of quinine should not be allowed to rise above 10 mg per litre. The serum half-life of quinine is prolonged in patients with hepatic or renal failure in whom the dose should be 10 mg/kg. For less seriously ill patients quinine can be given by mouth in a dose of 540 mg (2 tablets) every 8 hours for at least 4 doses depending on clinical response. A recent report recommends that quinine therapy of chloroquine-resistant MT malaria should be followed by a single dose of pyrimethamine (50 or 75 mg) combined with sulphadoxine (1 or 1.5 g) [Hall et al, 1975a]. These compounds both have very long plasma half-lives of over 100 hours. Other drugs which have been studied in chloroquine-resistant falciparum malaria include tetracycline (Colwell et al, 1972), clindamycin (Hall et al, 1975b), co-trimoxazole (Rollo, 1975) and mefloquine (Hall, 1975). None, however, have proven superiority over quinine.

Whereas benign tertian malaria responds rapidly to treatment and complications are rare, malignant tertian infections can be complicated by hepatic and renal failure, encephalopathy and disseminated intravascular coagulation (DIC). Heparin therapy has been recommended for the last named condition, but recent experience (Hall, 1975) suggests that heparin is not of value for DIC complicating falciparum malaria. Blackwater fever (acute haemolytic anaemia with haemoglobinuria) is treated with corticosteroid drugs. Fortunately this complication, which may be associated with renal failure, is rare.

Amoebiasis

Anti-amoebic drugs may act against *Entamoeba histolytica* either in body tissues or in the bowel lumen or in both. Emetine is a very effective 'tissue' amoebicide but is ineffective in eradicating amoebae from the intestine. Following emetine therapy, diloxanide furoate 500 mg three times a day for 10 days or metronidazole (see below) must be given for this purpose. Similarly, chloroquine is a useful *hepatic* 'tissue' amoebicide but has little effect in amoebic dysentery. However, metronidazole (Flagyl) is both a 'tissue' and 'contact' amoebicide and is the drug of choice for the treatment of all forms of amoebiasis, although there has been a suggestion that metronidazole is not particularly efficient in clearing amoebae from the bowel (Herrera-Llerandi, 1975). There is no available parenteral prepara-

tion of metronidazole, although there is one on clinical trial, and emetine therefore remains the most effective *parenteral* tissue amoebicide.

Emetine is a cardiotoxic drug and almost invariably produces changes in the electrocardiogram during therapy and can occasionally cause cardiac arrhythmias. Dihydroemetine is less toxic than emetine hydrochloride. The dose of emetine is 1 mg per kg body weight per day for 10 days, the total daily dose not exceeding 60 mg.

Metronidazole is given for the treatment of amoebiasis in a dose of 800 mg three times a day for 5-10 days. Alcohol most not be taken at the same time as metronidazole which has a pharmacological action similar to that of disulfiram (Antabuse).

If an amoebic liver abscess is suspected it should be localised by a radioisotope scan and aspirated through a wide-bore needle.

Giardiasis

Giardiasis is treated with metronidazole in a dose of 200 mg three times a day for 7 days. It may be necessary to repeat the course. An alternative drug is mepacrine in a dose of 100 mg three times a day, also for 7 days. Tinidazole in a single dose of 2 g (1 g for children) has also proved effective in the treatment of giardiasis (Petterson, 1975).

Trypanosomiasis

This infection is difficult to treat and wherever possible patients suffering from trypanosomiasis should be referred to a Tropical Diseases Centre. The African form of the disease is treated either with a metallic organic arsenical compound such as melarsen or tryparsamide, or alternatively by a non-metallic agent, e.g. suramin (which causes renal damage) or pentamidine (for *T. gambiense* infections only).

The South African form of the trypanosomiasis is extremly difficult to treat. There are certain compounds which are active against the trypanosomes in the blood but not against intracellular parasites.

Leishmaniasis

Visceral leishmaniasis (Kala-azar) is treated by a 10 day course of sodium stibogluconate (Pentostam) given by intravenous injection in an initial daily dose of 5 mg per kg body weight increasing to 10 mg per kg body weight. The dose for an adult should not normally exceed 600 mg per day.

Cutaneous leishmaniasis is fairly common in Asian immigrants in the United Kingdom and normally responds to local debridement of the lesion together with treatment of secondary infection, which is usually of staphylococcal aetiology. Large or multiple lesions may require parenteral Pentostam.

Bacterial and Rickettsial Infections

Enteric fever and brucellosis are the two most commonly imported bacterial infections. Although bacillary dysentery is often contracted by travellers, the short incubation period usually results in the patient developing symptoms while travelling. Similarly, cholera which has an incubation period of 1-3 days, is rarely diagnosed in the United Kingdom in spite of recent outbreaks in several Mediterranean countries patronised by British holiday-makers.

Patients occasionally arrive in this country suffering from leprosy. The diagnosis and treatment of this disease requires special experience and knowledge. Travellers' diarrhoea may be caused by a Salmonella species or an enteropathogenic *Escherichia coli* but in most instances stool cultures are negative for pathogenic bacteria.

Of the rickettsial infections which might be brought into the country by travellers, the typhus fevers are the most important, although fortunately rare.

Enteric Fever

The typhoid and paratyphoid fevers are regularly imported both by immigrants and holiday-makers. Chloramphenicol was the first drug to be effective in the treatment of typhoid fever but recent reports of chloramphenicol-resistant *Salmonella typhi* strains (Anderson & Smith, 1972; Lampe et al, 1974) have led to a search for alternative agents. Ampicillin is moderately effective in enteric fever but the response to treatment is slower than with chloramphenicol (Geddes & Murdoch, 1964). Amoxycillin, which differs from ampicillin only by one hydroxyl group, is better absorbed from the gastrointestinal tract than ampicillin and a recent report (Pillay et al, 1975) suggests that it may be as effective as chloramphenicol in typhoid fever. Further studies, however, are necessary to confirm this finding, especially as there is not a parenteral preparation of amoxycillin available for the treatment of very sick patients.

Co-trimoxazole is also an effective agent for enteric fever (Geddes, 1975) and the recent availability of a preparation for intravenous infusion has added to its usefulness in this condition. We have treated 51 patients suffering from typhoid fever and 14 from paratyphoid fever with co-trimoxazole. Sixty-two of these 65 patients have responded satisfactorily to therapy.

Mecillinam is a new amidino-penicillanic acid antibiotic which is highly active against salmonellae and has been used successfully in the treatment of typhoid fever (Limson, 1973). We have treated a very small number of patients suffering from typhoid fever with mecillinam and our results to date confirm this finding. There is a parenteral preparation of this antibiotic.

The chemotherapy of acute enteric fever must be continued for at least 14 days. Three grams of chloramphenicol should be given daily in 6 hourly divided doses until the patient begins to respond when the dose can be reduced to

500 mg 6 hourly. The dose of co-trimoxazole should be 240 mg of trimethoprim and 1200 mg of sulphamethoxazole given 12 hourly, reducing to 160 mg of trimethoprim and 800 mg of sulphamethoxazole when clinical response is obtained. Amoxycillin is given in a dose of 1 g 6 hourly.

Complications of enteric fever include perforation of, and haemorrhage from, the small bowel. There has been controversy as to the best method of treating intestinal perforation in typhoid fever but recently surgery has been strongly advocated with a marked reduction in mortality (Welch & Martin, 1975). Corticosteroids are occasionally indicated in patients with typhoid fever who are prostrated and very toxic.

Typhoid carriers should be treated for 12 weeks with either co-trimoxazole in a dose of 2 tablets twice a day (with regular monitoring of blood counts) or amoxycillin 500 mg four times a day plus probenecid.

Bacillary Dysentery

Bacillary dysentery caused by *Shigella sonnei* usually responds to symptomatic therapy and antibiotics are not normally indicated. Infections caused by *Shigella flexner* and *Shigella dysenteriae* produce marked systemic upset, and occasionally septicaemia, and the duration of symptoms and toxicity are reduced by co-trimoxazole therapy (Geddes, 1975).

Cholera

Intravenous fluid therapy is the mainstay of the treatment of cholera although experience has proved the value of oral replacement therapy using glucose and electrolyte solutions, the glucose enhancing intestinal sodium and water absorption (Nalin, 1975). Oral rehydration is principally indicated when intravenous therapy is impractical, e.g. in the field. Tetracycline in a dose of 250-500 mg given by mouth reduces the duration of diarrhoea in patients suffering from cholera.

Brucellosis

Acute brucellosis is treated by tetracycline in a dose of 500 mg four times a day continued for 21 days and, if treatment is started early enough in the illness, this will usually produce a cure. Delay in diagnosis makes treatment increasingly difficult. An alternative to tetracycline is cotrimoxazole which appears to be particularly effective in chronic brucellosis (Kontoyannis et al, 1975).

Travellers' Diarrhoea

As the majority of travellers' diarrhoeas are of non-bacterial aetiology chemo-

therapy is not normally indicated and a bowel sedative such as codeine phosphate 30 mg 8 hourly, combined with a fluid diet, effects a cure in most instances. Similarly, *non-invasive* Salmonella infections do not require specific chemotherapy, and indeed there is some evidence (Joint Project, 1970) that oral antibiotics may prolong faecal excretion of the infecting organism.

Typhus Fevers

The typhus fevers respond satisfactorily to tetracycline given in an initial dose of 500 mg 6 hourly reducing to 250 mg 6 hourly when toxicity lessens. Doxycycline is an alternative.

Leprosy

The management of this chronic mycobacterial infection requires specialised knowledge. Dapsone, which is slow-acting and bacteriostatic, is still widely used although dapsone resistance is now well recognised (Pearson et al, 1975). Recent advances in the treatment of leprosy include the new agent clofazimine (Lamprene), which is anti-inflammatory as well as anti-lepromatous, and is thus valuable in patients who have developed untoward reactions to dapsone. The antibiotic rifampicin is highly bactericidal against *Mycobacterium leprae* and can thus render the patient non-infectious within a very short time (Browne, 1975).

Helminth Infections

Immigrants from Asian countries are not infrequently infested with various helminths, particularly *Ascaris lumbricoides, Ankylostoma duodenale* and *Trichuris trichiura* and these three parasites quite commonly co-exist in the bowel. Other helminth infections likely to be contracted during travel include tapeworm, strongyloides, liver flukes, filariasis and schistosomiasis.

Helminth infections are often difficult to eradicate although some worms are more susceptible to treatment than others. Repeated courses of therapy may be necessary before eradication is achieved. Certain anthelminthics are active against only one worm while others have a moderately broad spectrum. Bephenium hydroxynaphthoate (Alcopar), for example, is effective against both ascaris and hookworm while thiabendazole is active against many round worms, including ascaris and strongyloides. Mebendazole is a recently introduced thiabendazole analogue under clinical trial which has a wide spectrum of activity and is active against *Ascaris lumbricoides, Trichuris trichiura,* taenia, enterobius, hookworm and, to a lesser degree, Hymenolepsis species (Hutchison et al 1975). It is therefore a useful drug for multiple worm infections.

Schistosoma haematobium infections are quite common in Arabian immigrants

in the United Kingdom, while *Schistosoma mansoni* can be contracted by travellers in the Middle East, Africa and Central and South America.

Roundworms

Piperazine phosphate in a single dose of 2 g for children and 4 g for adults, taken with the evening meal, paralyses *Ascaris lumbricoides* which is subsequently passed in the stool. A second dose given on the following day ensures a cure rate of 90 percent (Drug and Therapeutics Bulletin, 1975). Bephenium in a dose of 5 g for adults and older children, and half that dose for infants below the age of two, is also effective, as is thiabendazole in a dose of 25 mg per kg body weight to a maximum of 3 g daily and continued for 10 days. Mebendazole, 100 mg twice a day for 3 days causes fewer side-effects than thiabendazole. Unwanted effects of thiabendazole include nausea, drowsiness and vertigo, while bephenium and piperazine occasionally cause diarrhoea, vomiting and abdominal pain. Piperazine salts can also cause ataxia.

Tapeworms

Niclosamide (Yomesan) has a direct toxic action on all tapeworms although it is only moderately effective against *Hymenolepsis nana* (the dwarf tapeworm). Niclosamide is best given in the morning before food. Two tablets, each containing 500 mg followed by another 2 tablets one hour later, are chewed and swallowed with water before breakfast. Very little is absorbed and side-effects are therefore unusual, apart from minor gastrointestinal upset. For *Hymenolepsis* infections more prolonged treatment is required and 1 g daily is given for a further 6 days.

Hookworms

Bephenium hydroxynaphthoate in a single dose of 5 g of the salt (2.5 g for infants under two) is effective in most *Ankylostoma duondenale* infections. To be certain of a cure 2 or even 3 consecutive daily doses should be given. Mebendazole is possibly as effective as bephenium. Tetrachlorethylene is more toxic than bephenium but is cheaper and probably more effective against *Necator americanus.* Side-effects of bephenium include diarrhoea, vomiting and abdominal pain.

Schistosomiasis

Treatment should be supervised if possible by a tropical medicine specialist. Antimony compounds such as Stibophen, Astiban and Tartar emetic were until recently the drugs of choice for the treatment of schistosomiasis. These