Currently the greatest complaint from our women concerns their having to attend hospital antenatal clinics for what appear to them to be unnecessary consultations. Most of these and their content merely duplicate care already provided by the general practitioner and his team in the community. It is doubtful whether any low risk women (roughly three quarters of all pregnancies) who are booked for delivery in a general practice or specialist unit need to be seen at hospital at all, except perhaps for a scan at 16 weeks and a consultation at 36 weeks if the specialist unit is to be responsible for the delivery. Patently this will be a comprehensive assessment to note that all has gone well during the pregnancy and is normal for that particular period of gestation. At the same time women can be introduced to the unit in which they are to be delivered and meet appropriate members of the staff. Certainly patients in this practice who are experiencing our new style limited care and compare it with the more traditional systems in earlier pregnancies are extremely grateful and enjoy the considerable saving in time and effort in already busy lives.

These limited protocols produce a much more individual and cost effective style of care. They are far more appropriate to antenatal care in the 1980s than the traditional and dated system still almost universally in use.

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Research from the South

Treatment of tetanus: an open study to compare the efficacy of procaine penicillin and metronidazole

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Abstract

A prospective, open, non-randomised clinical trial was carried out to compare the efficacy of procaine penicillin with metronidazole in the treatment of moderate tetanus among 173 patients. Patients in the metronidazole group had a significantly lower mortality rate, a shorter stay in hospital, and an improved response to treatment. These results establish the value of antimicrobial treatment in the management of tetanus and show that metronidazole is more efficacious than penicillin in this respect.

Introduction

Tetanus is an infective disease that usually results from the contamination of a wound by *Clostridium tetani*. It commonly presents with rigidity of the muscles of the neck and trunk and generalised reflex spasms. These are pharmacological effects that are due to the exotoxin, tetanospasmin, produced by the organism (Abdulrahim, paper presented at symposium on anaerobic infection, medical faculty of University of Jakarta, Indonesia, 1984).[1,2] Although tetanus is entirely preventable by active immunisation, a high mortality rate of around 45% makes tetanus a serious problem in developing countries where active immunisation is not universally practised.

The management of tetanus aims to provide supportive care until the neurotoxin fixed to nervous tissue has been eliminated and to prevent the absorption of further toxin by giving antitoxin and by eradicating the organism, the source of the toxin.

Although there is no clear evidence about the value of antimicrobial treatment directed against the causative organism in the treatment of tetanus, antibiotics are invariably given for this purpose; it is with the eradication of the organism by antimicrobial treatment that the present study is concerned.

During the past decade metronidazole has emerged as a highly effective agent for both treating and preventing a wide variety of anaerobic bacterial diseases. It is an inexpensive, stable, and readily available drug that rapidly achieves therapeutic concentrations in virtually all body tissues and fluids (including abscess cavities) after rectal, oral, and intravenous administration. It is compatible with all other antimicrobial agents and is rapidly bactericidal for all anaerobic micro-organisms.[1] Unlike many other agents that show in vitro activity against *Cl tetani*, however, it is non-toxic, and its activity in vivo is not prejudiced by such factors as pH (as are, for example, erythromycin and lincomycin), or inactivating enzymes (as are, for example, β-lactam agents). Moreover, its narrow spectrum of activity (it is inactive against aerobes and facultative anaerobes) ensures that conventional courses of the drug do not interfere with normal bacterial floras and do not induce suprainfection. Resistance to metronidazole is rare. It has been used successfully in preventing and treating experimental tetanus in mice.[3]

Thus for the management of tetanus metronidazole seems to fulfil the basic requirements of rational, effective, and safe treatment (Abdulrahim, paper presented at symposium on anaerobic infec-

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tion, medical faculty of University of Jakarta, Indonesia, 1984). Moreover, the highly individual properties of this drug suggest that its use as a therapeutic probe may provide clear evidence of the value of antimicrobial treatment in general in this clinical setting.

We present the findings of a prospective, open, non-randomised clinical trial designed to compare the efficacy of procaine penicillin and metronidazole in the treatment of established tetanus.

Patients and methods

A prospective study was carried out for 12 months to May 1984 at the departments of surgery of the University of Indonesia and the Dr Cipto Mangunkusumo Hospital, Jakarta. All patients admitted with a clinical diagnosis of tetanus were considered for inclusion in the study. The severity index of each case was determined according to the variables suggested by Phillips,[4] and only those who scored within the range 9-19 (disease of moderate severity) were accepted into the trial. Patients whose severity index exceeded 19 were regarded as having severe intoxication, and it was considered unethical to include them in the study. Patients whose score was <9 had mild intoxication, from which spontaneous recovery should occur, and they were also excluded. Exclusions from the moderately severe index group included those patients who required immediate artificial ventilation and those who required antimicrobial treatment other than that permitted by the trial protocol.

Patients admitted into the trial were allocated to one or other of two antimicrobial treatment groups. In one group patients received procaine penicillin 1·5 MU intramuscularly eight hourly; in the other group patients received metronidazole 500 mg orally six hourly or 1 g rectally by suppository eight hourly. Antimicrobial treatment was continued for 7-10 days.

The general management was essentially the same for each patient. Suspected wounds were excised or debrided immediately and samples taken for microbiological study. Tetanus antitoxin 20 000 units intramuscularly was given immediately and repeated daily for five days. Patients were nursed in a quiet semi-darkened room with full nursing care. Special attention was paid to the prevention of pressure sores and muscle contracture. Oxygen was given and tracheostomy performed as necessary. Intravenous fluids were given to maintain the fluid and electrolyte balance until the patient was able to take nutrients orally. The duration of treatment with intravenous fluids was usually about 72 hours. To reduce reflex muscle spasm and muscle rigidity patients received phenobarbitone 100 mg intramuscularly, chlorpromazine 25 mg intramuscularly, and diazepam 10 mg intravenously eight hourly.

The criteria for assessing the efficacy of the antimicrobial treatment regimens were mortality, duration of nursing care, and the progress and response to treatment according to the criteria defined by Phillips.[4] The factors for determining the course of the disease were the severity of spasm, frequency of spasm, body temperature, and respiration rate. Inevitably, the assessment of these variables was much more subjective than for those determining the severity index. For the purposes of comparison the total score awarded for both the severity and the clinical course and response to treatment were considered to have a similar prognostic meaning.

Results

Altogether 222 patients with tetanus were admitted to hospital during the period of the study, 49 of whom were excluded as they did not meet the criteria for inclusion. Of the 173 patients included in the trial, 76 received procaine penicillin, and 97 metronidazole. The two treatment groups were statistically comparable in terms of age and sex, the various factors determining the severity index (table I), and the severity index itself on admission (table II).

The isolation rates of *Cl tetani* from suspected wounds among patients in the two treatment groups were similar (table III). This is in agreement with our own earlier experience and with published reports, in which only 30-60% of patients with tetanus had a positive culture result for *Cl tetani*. For this reason, and because the organism may also be isolated from the excised wounds of patients not suffering from tetanus, the diagnosis of tetanus was based on the clinical findings without a need for bacteriological confirmation.

The mortality rate in the metronidazole treatment group was significantly lower than that in the conventional treatment group (table IV). Thus 18 (24%) of 76 patients given penicillin died compared with only seven (7%) of 97 patients who received metronidazole. Among patients who survived in the two treatment groups admission to hospital was on average five days shorter with metronidazole than with penicillin (table V).

The progress of the disease and its response to treatment were also significantly better among patients who received metronidazole (tables II and VI). The course/response (table VI) scores were derived from the clinical assessment on the fifth day of treatment. Thus whereas 54 (56%) of 68 patients in the metronidazole group improved during the course of treatment only 28 (37%) of the 54 patients in the penicillin group did so.

TABLE I—*Distribution of factors determining the severity index among patients treated with penicillin or metronidazole. Figures are numbers of patients*

Factor	Penicillin	Metronidazole	Total
Incubation period:			
<2 days	0	1	1
2-5 days	17	22	39
6-10 days	45	35	80
11-14 days	5	20	25
>14 days	9	19	28
Site of infection:			
Umbilicus	0	1	1
Head neck	9	16	25
Torso	0	1	1
Upper extremities (proximal)	3	2	5
Upper extremities (distal)	8	13	21
Lower extremities (proximal)	1	1	2
Lower extremities (distal)	49	56	105
Unknown	6	7	13
State of immunisation:			
None	55	73	128
Possible	20	21	41
>10 years ago	0	2	2
<10 years ago	1	0	1
Complete immunisation	0	1	1
Complicating factors:			
Life threatening trauma	0	0	0
Severe trauma not threatening life	1	0	1
Moderate trauma	7	6	13
Mild trauma	64	80	144
ASA grade 1	4	11	15
Total	76	97	173

ASA = American Society of Anaesthetists.

TABLE II—*Severity index before treatment among patients treated with penicillin or metronidazole. Figures are numbers of patients*

Score	Penicillin	Metronidazole	Total
9-15	22	29	51
16-19	54	68	122
Total	76*	97*	173

*p>0·08 (χ^2 test).

TABLE III—*Isolation of Clostridium tetani from 132 suspected wounds among patients treated with penicillin and metronidazole. Figures are numbers (%) of patients*

	Penicillin	Metronidazole	Total
Cl tetani isolated:			
Yes	43 (73)	50 (68)	93
No	16 (27)	23 (32)	39
Total	59*	73*	132†

*p>0·5, NS (χ^2 test).
†Appropriate specimens were not available from some patients since portals of entry were not known in 41 cases.

TABLE IV—*Mortality and recovery among patients treated with penicillin and metronidazole. Figures are numbers (%) of patients*

Treatment group	Died	Recovered	Total
Penicillin	18 (24)*	58 (76)	76
Metronidazole	7 (7)*	90 (93)	97
Total	25	148	173

*p<0·01 (χ^2 test).

Discussion

The treatment of tetanus has three primary objectives: (*a*) to overcome disturbances in the body due to the tetanus toxin already bound to the central nervous system; (*b*) to neutralise toxin still circulating in the blood; and (*c*) to eradicate the tetanus bacillus itself. The general management of patients with tetanus involves the control of reflex spasms, the prevention of intercurrent infection, the control of fluid and electrolyte balance, and the maintenance of

the patients strength. The key to controlling muscle spasm is sedation and muscle relaxation. In cases of mild or moderate severity this may be achieved by a combination of treatment with drugs such as phenobarbitone, chlorpromazine, and diazepam. In more severe cases, however, total paralysis by curarisation and application of intermittent positive pressure ventilation in the tracheostomised patient is usually required.

TABLE V—*Duration of hospital stay of survivors treated with penicillin or metronidazole. Figures are numbers (%) of patients*

Duration (days)	Penicillin	Metronidazole	Total
1-10	15 (26)	37 (41)	52
11-20	23 (40)	40 (44)	63
21-30	15 (26)	12 (13)	27
31-40	5 (6)	1 (2)	6
Total	58*	90*	148

*$p<0.001$ (Student's t test).

TABLE VI—*Course of disease and response to treatment among patients treated with penicillin or metronidazole. Figures are numbers of patients*

Score	Penicillin	Metronidazole	Total
9-15	50	83	133
16-30	26	14	40
Total	76*	97*	173

*$p>0.01$ (χ^2 test).

In our units we classify tetanus into three categories of severity according to the notational system developed by Phillips,[4] which enables decisions to be taken about the method of treatment and the likely outcome of the disease in individual patients. In Phillips' system the severity of tetanus is assessed by assigning a score to each of four variables: incubation time, site of infection, state of immunity, and complicating factors. The summation of these scores provides the severity index, which classifies the disease into mild (score <9), moderate (score 9-19), and severe tetanus (score >19). Patients with severe tetanus are nursed in the intensive care unit and are closely monitored for respiratory disturbances such as laryngeal spasm and retention of secretion. Steps are taken to reduce the risk of aspiration, and facilities are at hand for endotracheal intubation, mechanical ventilation, tracheostomy, and total paralysis with curarisation and intermittent positive pressure ventilation. In this group with severe tetanus we also include elderly patients, those with cardiovascular disturbances such as labile hypotension and cardiac arrhythmias, those with hyperpyrexia, those with evidence of respiratory insufficiency of late onset, and those who have severe attacks of muscle spasm with dyspnoea and cyanosis uncontrolled by sedatives. After the start of treatment the subsequent course of the disease and the response to treatment are further assessed by the notational system of Phillips[4] by awarding a score to each of a further four variables: severity of spasm, frequency of spasm, body temperature, and respiration. As with the initial prognostic severity index, the summation of these scores provides an index of progress. Using the guidelines outlined above, together with modern methods of careful nursing and complex intensive care techniques for the general support of the patient, we have been successful in reducing the morbidity and mortality of tetanus as judged from our own earlier experience and from published data.

Neutralisation of circulating toxin is achieved by the administration of tetanus antitoxin or human tetanus immunoglobulin; because the second is not readily available to us we use heterologous antitoxin. Although there is no absolute certainty about the value of antitoxin in the treatment of tetanus, its use remains justifiable on the grounds that it will neutralise circulating "unfixed" toxin and thus prevent progression to a more severe intoxication. We give antitoxin in a dose of 20 000 units daily for five consecutive days, a schedule that is considered by many to be excessive but is certainly adequate.

Eradication of the infecting organism is achieved in our units by surgical treatment of the suspected wound, supported by penicillin treatment; in the absence of a wound (idiopathic tetanus) reliance must be placed on antibiotic treatment alone. The rationale of wound treatment is based on the assumption that the production of toxin by the infecting organisms is a continuous process, which can be interrupted only by removal or destruction of the tetanus bacilli.[5,6] Neither surgical treatment (especially wound excision) nor antimicrobial treatment is recommended by all workers.[7]

Despite our endeavours in these three main areas of management, both the morbidity and mortality among our patients have remained unacceptably high. When reviewing our management procedures we were made aware of the possible ineffectiveness of the fairly conventional schedule of antimicrobial treatment used. The efficacy of antibiotics depends not only on the sensitivity of the infecting strains to the drug but also on the concentration of the drug attained and sustained at the site of infection. Because the infected wound in tetanus is essentially anaerobic the target site is unlikely to receive therapeutic concentrations of many drugs such as penicillin since they depend on adequate perfusion for delivery to the tissues. Moreover, the presence of concomitant infecting or colonising β-lactamase producing organisms such as staphylococci and *Escherichia coli* would ensure that what little penicillin does find its way into the infected zone is promptly inactivated by enzyme activity.[8] These considerations led us to question seriously the efficacy of the antimicrobial management of our patients, and we decided to re-evaluate it against the established gold standard for anaerobic sepsis—namely, metronidazole.

It has been shown repeatedly that metronidazole is rapidly bactericidal both in vitro and in vivo against the whole spectrum of anaerobic organisms and that its pharmacokinetic attributes ensure its distribution at effective therapeutic concentrations even to anaerobic tissues. Moreover, the drug has been used successfully in preventing and treating experimental tetanus in mice and seems to be more active in this setting than penicillin and tetracycline.[3,8] In the present study all of the relevant comparisons made between the two patient groups—mortality, progress of disease, and length of hospital stay—showed that those who received metronidazole had statistically significantly better results than those who received penicillin. A comparison between penicillin and metronidazole was chosen for two reasons. Firstly, since antimicrobial treatment is widely accepted, at least as an adjunctive element, in the management of tetanus it would be unethical to use an inactive placebo for control purposes. No such objection can be raised against the pair of drugs used in the present study. Thus penicillin is widely accepted as a first line agent for use in preventing and managing most clostridial infections (including tetanus), whereas metronidazole (the test drug in this study) is the established drug of choice for the prophylaxis and treatment of anaerobic infections in general. Secondly, since metronidazole is virtually totally inactive against aerobes and facultative bacteria any benefits accruing from its use may be confidently attributed to its specific anaerobicidal activity, which, moreover, is not interfered with by the presence of other bacterial species.

As a result of the present study antimicrobial treatment has been established as an important part of the management of tetanus, and metronidazole has emerged as the drug of choice. The clear therapeutic benefits of metronidazole suggest that the drug should also be of value in tetanus prophylaxis in compromised patients, and this is an area that we hope to investigate in the future.

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