Human brucellosis : An evaluation of antibiotics in the treatment of brucellosis

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THE INTRODUCTION of antibiotics has undoubtedly been of great benefit to patients suffering from brucellosis. This has been the general experience of every physician dealing with the management of this disease. The precise role of antibiotics in the treatment of brucellosis, however, has not been established; most recommendations regarding type of antibiotic, dose and duration of treatment, have usually been based on reports of the response in small groups of patients or on a rather equivocal impression of the physician concerned.

There are very few, if any, large-scale surveys of this particular problem and we thought that a review of the records of 508 patients admitted with brucellosis to one of the medical units at St Luke's Hospital, Malta, from 1949 to 1964, might help in shedding some light on this problem.

Human brucellosis in the Maltese Islands is caused by *Brucella melitensis* and is usually contracted by the consumption of infected goat's milk (or milk products), which have not been pasteurized or adequately boiled. Other sources of infection are: contact with infected goat's meat, as in butchers and slaughterhouse men, and through living in close contact with goats—a common occurrence in rural areas. Mass pasteurization of milk and other sanitary measures have cut down the incidence of the disease, which is now very much reduced and practically restricted to rural areas.

Brucellosis is also being brought under control in many other parts of the world, but that it is still a problem in many countries can be seen by a glance at the brucellosis section of the World Health Organization Epidemiological and Vital Statistics Report for 1966.

Brucellosis is not a notifiable disease in the United Kingdom but the existing problem has been well defined by several authors. Dalrymple-Champneys (1960) estimated the incidence at over 1000 cases a year. Bothwell (1963) has also emphasized the problem of brucellosis in the U.K. The disease in the U.K. is caused by *Brucella abortus*. Cattle are the main hosts for *Brucella* in the U.K., although isolated cases occur in sheep, horses, deer and rats; the incidence in cattle has been estimated to vary from negligible in some districts to as high as 30% in others.

Scope of review

The number of patients included in the study and the antibiotic used are shown in Table 1. It is to be seen that the vast majority of the patients

TABLE 1
Number of cases included in study and antibiotic used

Drug	No. of cases
Tetracyclines	422
Chloramphenicol	50
Streptomycin	2
Novobiocin	4
Sulphadiazine	1
No chemotherapy	29
Total	508

Seventeen patients had combined streptomycin and tetracycline. These are included under tetracyclines.

Two patients had sulphadiazine with no effect and followed by aureomycin. Cases included under tetracyclines.

One patient had combined sulphadiazine and streptomycin. Case included under streptomycin.

Ampicillin was used in one case without effect. Case included under tetracyclines.

(422 out of 508) received one of the tetracycline group of drugs. The choice of the particular tetracycline very often depended on the availability of the antibiotic, and new antibiotics were tried as they came on the market. Chloramphenicol was, in the majority of instances, probably used when the clinical picture, on admission to hospital, suggested typhoid fever, and the diagnosis of brucellosis only made when the laboratory results were available.

Treatment was very varied during the period under review, especially during the earlier part. Various antibiotics were given for short or long periods. While the most usual period was for 14 days, the duration of treatment varied from under a week, in some cases, to over 20 days in others. For the purpose of this review, however, the duration of treatment has been classified as: under 10 days; 10–15 days, and more than 20 days. The occasional patient who had treatment for a period of 15–20 days was included in the nearest group. It is hoped that comparison of the results obtained with the various regimes of treatment may help in showing: (a) the more effective drug or drug combination; (b) whether short courses were as effective as longer courses in producing improvement and/or in reducing the number of relapses; (c) whether a small dose of the drug was as effective as a larger one; and (d) whether there were any factors, such as age, which affected the patient's response to treatment.

It is also hoped our results or conclusions may be compared with those of other workers interested in brucellosis and with the technical reports issued by the Joint Food and Agricultural Organization/World Health Organization Expert Committee in 1958 and 1964.

Criteria for diagnosis and inclusion of cases in review

Only patients with sufficient bacteriological proof or patients with good serological and clinical evidence of brucellosis have been included. A positive blood culture was taken as irrefutable evidence of brucellosis. Agglutination titres of very high values, e.g. 1 : 1280, were given great significance. The lowest titre that was accepted for the purpose of this study was 1 : 160 and it was only accepted if combined with satisfactory clinical evidence of brucellosis, such as prolonged fever, a history of consumption of unpasteurized goat's milk or milk products, or of living or working in contact with goats. Splenomegaly and leucopenia were considered as good supporting evidence, as were the presence of certain complications usually associated with brucellosis, such as bone and joint involvement and orchitis. The

absence of signs of other diseases, such as tuberculosis, which may simulate brucellosis was also considered in the diagnosis.

Criteria for assessment of results

The Joint FAO/WHO Expert Committee on brucellosis, in its fourth report (1964) suggested that in view of the frequency of spontaneous recovery, the following points were of value in judging the effectiveness of any therapy: (a) clinical recovery within a period of 1 week; (b) the failure to recover *Brucella* from the blood or from other tissues or sites previously positive; (c) a reduction in the incidence of complications; (d) a reduction in the frequency of relapses; and (e) a marked drop in agglutination titre.

These suggestions were used in expressing results of treatment, as follows:

(1) *Good*: A patient was assessed as having a good result if he or she showed a good clinical improvement within 1 week and did not relapse.

(2) *Poor response*: The antibiotic was assumed to have a poor response if the patient did not show any clinical improvement, or if blood culture remained positive after 1 week. The period of 1 week was taken from the Committee's suggestions (see above).

(3) *Relapse*: A patient was assumed to have relapsed if there was a good immediate effect, but again developed signs and symptoms of brucellosis. The same criteria were used for the diagnosis of a relapse as for the initial diagnosis, except that the agglutination titre was given less stress in the assessment of the case.

Follow-up period

All patients admitted to this unit with brucellosis are followed up in out-patients at regular intervals, for an indefinite period, certainly not less than a year. They are also asked to report immediately if they have any fever or other symptoms so that relapses are likely to be detected early.

Results obtained with antibiotic used

A total of 508 patients were included in the review (Table 1). Four hundred and twenty-two received one of the tetracyclines, fifty patients received chloramphenicol, twenty-nine did not receive any antibiotic at all, seventeen had combined treatment of streptomycin and tetracycline, and a small miscellaneous group received streptomycin, ampicillin or sulphadiazine alone.

The results of treatment are shown in Tables 2 and 3. There was only one death in this series of patients. He was a 48-year-old man, admitted with hyperpyrexia. Brucellosis was confirmed by positive blood culture. Thirty-two days after admission

TABLE 2
Result of treatment

Therapy	No. of adults	Good response (%)	No. of adults and children	Good response (%)
Tetracyclines duration 10-15 days	281	77.2	332	76.3
Tetracyclines duration more than 20 days	37	72	48	62
Tetracyclines duration less than 10 days	38	65.8	42	62
Chloramphenicol duration 10-15 days	33	57.6	36	58.4
Chloramphenicol duration less than 10 days	14	64.3	14	64.3
Streptomycin (usually used in combination)	14	71.4	18	61.1

TABLE 3

Number of patients in whom drug appeared to have no effect or who relapsed

Antibiotic therapy	Total No.	No appreciable effect (%)	Relapsed (%)
Tetracyclines 10-15 days	332	8.7	15
Tetracyclines 20 days plus	48	31.25	6.25
Tetracyclines less than 10 days	42	19	19
Chloramphenicol 10-15 days	36	19.4	22.2
Chloramphenicol less than 10 days	14	28.6	7.1
Streptomycin (combined)	18	33.3	5.6

and, when he had apparently recovered as a result of tetracycline treatment, he developed signs of a stroke and died soon afterwards. The cause of death was put down as subarachnoid haemorrhage; a post-mortem examination was not carried out.

Streptomycin

Spink (1960), in a report to the Council of Drugs (U.S.A.), suggests that in more severe cases streptomycin 1-2 g daily should be given simultaneously with a tetracycline. This recommendation was also made by the Joint FAO/WHO Committee in their technical reports (1958 and 1964). It is difficult to draw firm conclusions from

such a small group of patients (eighteen). In our series of patients streptomycin was given in a dose of 1 g daily for 14 days. It was never given alone. One patient received streptomycin combined with sulphadiazine with no effect after 12 days. Seventeen patients received streptomycin with a tetracycline, the latter being continued for a minimum period of 21 days, in all patients, except two. It is interesting to note that in these two patients there was a poor response. When all the cases are considered, however, it is also seen that the addition of streptomycin, whilst increasing the risk of toxicity, has not been of much use to the patient. This further strengthens our general impression (Ganado, 1965) that streptomycin, used either alone or in combination, is not of great value in brucellosis.

Chloramphenicol

The total number of patients who received chloramphenicol was fifty; the adult dose generally used was 2 g daily.

It can be seen from Tables 2 and 3 that chloramphenicol has some effect in brucellosis but it is also obvious that it is the least effective of the antibiotics used in this series of patients. Only 58.4% of the patients who had chloramphenicol for a 10-15-day period had a good response, against 76.3% of patients who had tetracyclines in the same dosage for the same period. It is also seen from Table 3 which considers the failures that chloramphenicol has the highest relapse rate (viz. 22.2% of the patients taking the drug for a 10-15-day period). Chloramphenicol has, moreover, very serious toxic effects on the bone marrow, occasionally producing aplastic anaemia, agranulocytosis and thrombocytopenia. This toxicity of chloramphenicol may be a serious complication in the treatment of brucellosis in which the drug is administered for either long or intermittent periods. For these reasons and for the fact that it is less effective than the tetracyclines, the use of chloramphenicol cannot be recommended as a drug of first choice. These conclusions are in general agreement with those of other workers, notably Dalrymple-Champneys (1960) and the Joint FAO/WHO Expert Committee on Brucellosis in their third report.

Novobiocin

Novobiocin was used in four cases; it had no effect in two cases, whilst clinical improvement followed its use in the other two. Two of those patients developed severe reactions and drug rashes at about the 7th day. Torres (1958) reported very favourably on this drug but his results were not substantiated by Debono (1958), who reported

severe reactions and drug rashes in seven out of his twenty-two patients, and five relapses (bacteriological) out of the other fifteen. Debono's results were confirmed by others (Aznar & Lopez, 1959; Farid *et al.*, 1963). Novobiocin cannot, on these grounds, be recommended in the treatment of brucellosis.

Tetracyclines

The vast majority (422) of patients in this review received one of the tetracyclines. The bulk (332) received a tetracycline for a period of 10–15 days. Forty-eight of the remainder received tetracyclines for more than 20 days, while the rest (forty-two) received tetracyclines for less than 10 days. Results obtained with the three regimes of treatment were compared in order to assess the importance of the duration of treatment. Reference to Table 2 shows that, *prime facie*, the best over-all results were obtained in patients who received tetracycline for a period of 10–15 days (recovery rate 76.3%). Patients who received tetracyclines for a period of more than 20 days or for less than 10 days show a recovery rate of only 62%. If only adults are considered, however, the recovery rate becomes 77.2% for the 10–15 days group, 72% for the 20 days-plus and 65.8% for the <10 days group.

When the failures are considered separately, it is seen that the majority of patients, fifteen out of eighteen, who did not recover in the 20 days-plus group, are in the 'poor-response' column, which is the reason why they were given treatment for this length of time and certainly would not have responded to only 10–15 days treatment. This explains the paradoxical results obtained, viz. that patients who had 10–15 days treatment fared better than those who had treatment for more than 20 days. As a consequence, no weight can be put on the recovery figures. The important point to note in the group of patients who had tetracyclines for more than 20 days is that they have the lowest relapse rate of all the groups, 6.25% (cf. 15% in the 10–15 days group and 19% in the <10 days groups). A case can therefore be made from these figures for giving tetracyclines for a minimum period of 21 days, as suggested by Spink (1960) and by the Joint FAO/WHO Expert Committee.

The indiscriminate use of tetracyclines in brucellosis, however, is not advisable as they have their own disadvantages and toxic effects. An important side effect which has to be taken into account in children is discoloration of the teeth (Weyman, 1965). Clinical and experimental evidence (Owen, 1962; Wallman & Hilton, 1962) suggest that the least objectionable staining of the teeth is produced by oxytetracycline; this antibiotic is preferable in children. The advantages of

using tetracyclines for brucellosis in children must obviously be weighed very carefully against this aesthetically unpleasant effect.

Cases which improved spontaneously without antibiotics

Twenty-nine patients of the total of 508 did not receive any antibiotics; all these patients recovered over a longer or shorter period. Some of these patients, bacteriologically positive, were admitted with fever and discharged after a few days, because their fever and symptoms had subsided. These were followed up and remained well. The frequency of spontaneous, and sometimes sudden, recovery in brucellosis has been stressed by Dalrymple-Champneys (1960) and is also mentioned by the Expert Committee (1958 and 1964). The fact has to be strongly considered before starting treatment with antibiotics.

Relationship of age of patient and response to chemotherapy

Table 4 (a, b and c) shows the ages of all the patients taking tetracycline and the ages of all the patients who failed to respond to the drug. It is

TABLE 4
Age distribution of patients on tetracyclines

Age (years)	No. of cases	Good response (%)	Poor response (%)	Relapse (%)
(a) Duration of therapy 10–15 days				
<10	49	69.4	26.5	4.1
11–20	133	79.1	4.5	16.4
21–30	62	77.5	3.25	19.25
31–40	31	74.5	0	25.5
41–50	26	73	15.4	11.6
51–60	18	77.8	5.6	16.6
61 plus	13	77	23	0
Total	332	76.3	8.7	15
(b) Duration of therapy more than 20 days				
<10	11	27.3	63.5	9.2
11–20	14	78.1	21.9	0
21–30	8	62.1	12.5	25
31–40	3	100	0	0
41–50	3	66.6	33.3	0
51–60	4	75	25	0
61 plus	5	60	40	0
Total	48	62.5	31.25	6.25
(c) Duration of therapy less than 10 days				
<10	4	25	75	0
11–20	16	56.25	12.5	31.25
21–30	12	91.8	8.2	0
31–40	5	60	20	20
41–50	2	50	0	50
51–60	2	50	0	50
61 plus	1	0	100	0
Total	42	62	19	19

seen from this table that the drug is least effective in children under 10 years of age, i.e. only 69.4% recovered in this age group against 79.1% in patients (11–20 years), taking the drug from 10–15 days. The recovery rate in the under 10-year group is also extremely low in patients taking the drug for more than 20 days, i.e. only 27.3%, cf. 78.1% in the 11–20-year group; again, in the other group of patients who received the drug for less than 10 days, only 25% recovered in the under 10-year age group against 91.8% in the 21–30-year group. Table 5 breaks up further the under 10-year group

TABLE 5

Patients under 10 subdivided into two groups

Age (years)	Total No.	Good response (%)	Poor response (%)	Relapse (%)
0–5	12	33.3	66.6	0
6–10	52	65.4	28.8	5.75

All the patients are considered together because of small numbers.

into under 5 and 6–10. It is seen that by far the lowest recovery rate is in the under 5, only 33.3%, cf. 65.4% in the 6–10-year group. If the failures of the under 10-year group are considered separately (Table 4a, b and c), the vast majority are in the 'poor response' column and not in the 'relapse' column: 26.5%, cf. 4.1% (Table 4a); 63.5%, cf. 9.2% (Table 4b); and 75%, cf. 0% (Table 4c). These figures show that children, especially those under 5 years, do not appear to respond to tetracyclines as well as adults. In this age group, moreover, the disease is, in our experience, often mild; other authors (Dalrymple-Champneys, 1960) concur in this. Spontaneous recovery is also quite common. For these reasons and because of their undesirable effects, in children tetracyclines should, if possible, be avoided.

The best results are in the 11–40 years, i.e. 79.1% (11–20 years), 77.5% (20–30 years) and 74.5% (30–40 years), but the interesting feature in these groups is that they have the highest number of relapses, viz. 16.4% (11–20 years), 19.25% (21–30 years) and 25.5% (31–40 years)—see Table 4(a). These patients must obviously be considered separately from children and a regime of treatment that will cut down the relapse rate is indicated.

Relationship of total dose and response of patient

Table 6 (a, b and c) shows the total dose received, the duration of treatment and the response of the patient. Although no very definite

TABLE 6

Total dose in grams and response to treatment

Dose (g)	No. of cases	Good response (%)	Poor response (%)	Relapse (%)
(a) Tetracyclines 10–15 days				
< 15	37	78.4	8.2	13.4
16–21	40	70	10	20
22–27	45	75.5	11.2	13.3
28–33	184	77.2	7.1	15.7
34–39	18	72.2	16.7	11.1
40 plus	8	87.5	12.5	0
Total	332	76.3	8.7	15
(b) Tetracyclines less than 10 days				
6–11	13	38.5	15.4	46.1
12–15	14	71.5	21.4	7.1
16–21	15	73.2	20	6.8
Total	42	62	19	19
(c) Tetracyclines more than 20 days				
20–21	10	50	40	10
24–26	3	33.3	66.6	0
32–36	5	60	20	20
40–42	17	58.8	35.3	5.9
50–60	9	77.6	22.4	0
61 plus	4	100	0	0
Total	48	62.5	31.25	6.25

conclusions can be drawn from Table 6(a), certain features may be pointed out; at a first glance, there appears to be an advantage in giving more than 2 g daily because the best results are obtained in the 40 g-plus group, i.e. 87.5%, but these results are offset by the next higher group, viz. 34–39 g which are poor (only 72.2%); again, those who received less than 15 g show a recovery rate of 78.4%. A look at the relapse column shows that slightly better results are obtained by increasing the dose to more than 2 g, but this slight advantage is probably easily offset by the increase of side-effects which are bound to occur with increase of dosage. Table 6(b) refers to patients who received tetracyclines for less than 10 days. The total dose appears to be important in this group of patients because of the group of thirteen who received about 1 g daily or less, only 38.5% recovered, whilst the groups of fifteen patients who received 2 g daily the recovery rate is nearly doubled (73.2%); the main difference lies in the relapse rate of the two groups (46.1% in the low dosage group against 6.8% in the higher dosage group). Table 6(c) refers to patients who received tetracyclines for more than 20 days. The total dose again appears to be significant in this group of patients. Patients in the upper part of the table, who received a lower dose, had worse results than patients in the higher dosage group.

Although the number of patients is not large, these last two tables indicate that the minimum adult dose is 2 g daily and that increasing the dose might improve the results of treatment.

Discussion

The tetracyclines are, at present, the antibiotics of choice in brucellosis. This is confirmed by our figures in this study which also agree with the recommendations made by other workers (Spink, 1960; Dalrymple-Champneys, 1960). The tetracyclines, besides being the most effective antibiotics against brucellosis, are, at any rate for adults, also the least toxic of the antibiotics reviewed in this series. Tetracyclines may also be repeated for relapses when these occur. Spink (1960) recommends a repetition of another 21 days of treatment, but goes on to say that it is doubtful whether more than three courses are beneficial to the patient. Figures for the treatment of relapses have not been produced but many of the relapses, bacteriologically positive, recovered spontaneously without any antibiotic treatment. Therefore, whilst a repetition of a 21-day course of tetracycline may not do much harm, it may also not do much good, and it is probably better to wait and watch the patient for the first few days before starting treatment.

The dose recommended is a minimum of 2 g daily for adults; there is some evidence, Table 6 (a, b and c), that an increase of this dose, if tolerated by the patients, may improve results both as regards immediate effects and relapse rate. Regarding the duration of treatment, tetracycline for a minimum period of 21 days is recommended in the age group 11–40 years who were shown, by our figures, to have the highest relapse rate. Our figures also show that when tetracyclines are given for a period of more than 20 days there is a significant lowering of relapse rate. Patients in other age groups should be treated on their own merits. Treatment in children under 5 years, in whom the disease is often mild with spontaneous recovery, should be mainly supportive and tetracyclines avoided if possible and reserved for the first signs of complications. Oxytetracyclines should be preferred in children.

Chloramphenicol should be avoided and never used as a drug of first choice. It has been shown to be less effective than the tetracyclines, both as regards immediate effects and relapses. The addition of streptomycin to tetracyclines did not appear to significantly affect our patient's response to treatment. Novobiocin has no place in the treatment of brucellosis. Sulphonamides were only used in two patients in this series in whom they

had no appreciable effect. It is the general opinion that, at the present time, sulphonamides, used alone, have no place in the treatment of brucellosis. Their use with other antibiotics has been difficult to assess.

It can be seen from the above that the antibiotic treatment of brucellosis is far from satisfactory. Many patients still do not respond whilst many others recover only to relapse later. The search for other antibiotics or chemotherapeutic agents must be continued. These drugs must not only be more effective than the antibiotics now available but also less toxic so that they can be given for long periods, because *Brucella*, in some patients, becomes entrenched and difficult to eradicate.

Ampicillin, unfortunately, does not appear to have any effect in brucellosis. It was tried on one of our patients in a dose of 2 g daily for a period of 6 days without success. The same result was obtained by Farid, Bassily & Omar (1964) when they tried it in two of their cases. Sharma (1965) has claimed considerable success when treating four cases of *Brucella abortus* with nalidixic acid (Negram), a drug recommended for urinary tract infections by Gram-negative organisms. This drug was found to be effective *in vitro* against *Brucella abortus* in the same concentration (10 µg/100 ml). The dose used was 1 g four times daily for 10 days. It remains to be seen, however, whether this success will be confirmed by others or whether it will prove more successful or less toxic than tetracycline. Vaccines and antigens have not been mentioned. They were used in some of the cases who failed to respond to the antibiotics; although they appear to be effective in some patients, their true value is difficult to assess. Vaccines are being used prophylactically for people at high risk.

It is stressed, however, that all these are temporary and palliative measures in controlling human brucellosis. Health and agricultural authorities should direct their main efforts towards the control and eventual eradication of animal brucellosis.

Summary

The record of 508 cases of brucellosis admitted to one of the medical units in Malta were reviewed and the results of various regimes of treatment compared. Tetracyclines, in an adult dose of 2 g daily, and continued for at least 21 days, appears to be the regime of choice.

The need for giving antibiotics, especially tetracyclines in children has been questioned.

The search for a more effective and less toxic antibiotic must be continued.

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