A REPORT ON THE USE OF TETANUS TOXOID IN THE MANAGEMENT OF TETANUS

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In 1935, Miller and Rogers wrote that "treatment (of tetanus) in general is hardly more satisfactory than when Hippocrates handled the cases at the battle of Salamis, or when, centuries later, Frederick May advocated the use of infusions of tobacco by rectum." Since then the mortality rate has decreased moderately, but is still high in developed and more so in underdeveloped countries, with most of the figures ranging from roughly 35% to 80% (Patel and Joag, 1959; Eckmann, 1963; Kloetzel, 1963; Saxena *et al.*, 1966; Bern, 1966). This improvement may be attributed to intensive nursing care, physiotherapy, the proper maintenance of fluid, electrolyte and nutritional balance, the surgical treatment of the entry wound, the administration of antibiotics, tetanus antitoxin, sedatives and anticonvulsants, the performance of tracheostomy and the use of skeletal muscle paralysis with intermittent positive pressure respiration (Diaz-Riviera *et al.*, 1951; Laurence *et al.*, 1958; Brown *et al.*, 1960; Wilkinson, 1961; Laurence and Webster, 1963; Bern, 1966; Gray and Dundee, 1966; Lancet, 1967). These measures are universally or widely used, though the value of some of them has been called in question (Eckmann, 1963; Adams *et al.*, 1966; Vaishnava *et al.*, 1966), and indeed in our experience locally the adoption of an allegedly superior therapeutic regime, namely, lytic cocktail consisting of chlorpromazine, pethidine and promethazine could result in an alarming rise in mortality rate from 21·1% to 52·9% and 39·3% in 1957 to 1958 and 1959 respectively (Gwee and Lee, 1962).

One possible therapeutic agent employed on only a small scale in the immediate management of tetanus cases is tetanus toxoid whose value in prophylaxis is undoubted (Scheibel, 1955; Edsall, 1959). We believe that it may have an important place in our therapeutic armamentarium, both on theoretical grounds and on the fact as reported below that with its routine use in Medical Unit III we have lost only two out of a preliminary series of eighteen patients. Admittedly, this is a small series and our results are by no means as impressive as those from specialised tetanus units like that in Leeds, where there were only two deaths in fifty-nine cases (Lancet, 1967). However our results are superior to those of most treatment centres and as far as we can ascertain they are certainly the best so far in Singapore (Gwee and Nadarajah, 1960; Gwee and Lee, 1962; Gwee, 1968). Locally the only comparable figure was the mortality rate of 15% obtained by the use of gamma butyric acid and by placing the cases under the care of the anaesthetic unit (Ganedran, 1964) but this series was a highly selected one.

MATERIAL AND METHODS

Our series consisted of 18 consecutive case admitted to our unit from March 1966 to February 1968 (see Table I). There were 15 Chinese, 2 Malays, and 1 Indian; their ages ranged between 12 and 68 years; and males predominated over females in a ratio of 13 to 5. They were isolated in darkened, quiet, cool rooms and special nurses were assigned to them. The entry wound was treated surgically if indicated. Phenobarbitone was given initially in a dose of 250-400 mg. daily, increasing to a maximum of 800 mg. daily; chlorpromazine was given initially in a dose of 100-200 mg. daily, increasing to 400 mg. daily; and diazepam was started and maintained at a dose of 40 mg. daily, except in case 12 (see Table 1) who received up to 320 mg. daily. Two of these drugs were given every 4 hours by rotation, usually via a nasogastric tube and if necessary intramuscularly or intravenously. Crystalline penicillin was given in a dose of 1 mega 6 hourly intramuscularly. Early on in our trial, a dose of only 20,000 i.u. of equine anti-toxin intra-

muscularly was used (Vakil *et al.*, 1963, 1964; Lucas *et al.*, 1965), but later we used 50,000 i.u. intramuscularly and 50,000 i.u. intravenously. 0·5-1 ml. of tetanus toxoid intramuscularly was also given immediately, the adsorbed preparation being used in preference to the fluid preparation (Trinca, 1965). Tracheostomy was done on half of the patients for respiratory distress due to laryngeal spasm, pneumonia or accumulation of secretions in the air passages, or as an elective procedure in severe cases. Curarisation and intermittent positive pressure respiration were employed only in case 9 (see Table I) without averting a fatal result.

RESULTS

Three prognostic categories were used:-

(a) Severe, i.e. patients with generalised reflex spasms occurring at least once every 5 minutes.
(b) Moderately severe, i.e. patients with less frequent spasms.
(c) Mild, i.e. patients with no generalised spasms.

Six of our cases were severe, 5 moderately severe, and 7 mild. Our 2 deaths (cases 1 and 9 in Table I) who were both Chinese males, belonged to the severe category. Taking the moderately severe and the severe cases together, the mortality rate was 18.2%. The overall mortality rate was 11·1%. If we employ the method of grading recommended by Patel and Joag (1959) with grades 1 to 5 carrying expected mortality rates of 0%, 10·3%, 32·5%, 61·8% and 83·5% respectively, it will be seen from Table I that 1 belonged to grade 5, 6 to grade 4, and 3 to grade 3, our mortality rate in these 3 grades being 20% on average.

DISCUSSION

Whether tetanus toxin acts centrally on the neurones of the spinal cord and brainstem or peripherally on the neuromuscular junction and whether the toxin is transported by nervous pathways or by the blood stream have been hotly disputed questions but the evidence on the whole seems to favour the central action of tetanus toxin spread neurally (Marie and Morax, 1902; Meyer and Ransom, 1903; Abel *et al.*, 1935, 1936, 1938; Laurence and Webster, 1963; Rose, 1963; Bern, 1966). In the central nervous system the gangliosides are the receptors for the toxin (Van Heyningen, 1959, 1961).

The first theoretical consideration for the immediate administration of tetanus toxoid in the management of tetanus patients is based on the close structural similarity between the toxoid and toxin and it is possible that by the process of competitive fixation the toxoid can protect the gangliosides of the central nervous system from the damaging contact of the toxin. In practice, some clinical studies seem to vindicate this theory (Eckmann, 1963).

The second reason for this method of treatment is that though it is well known that tetanus infection by itself does not give rise to immunity, it may form the basis for a substantial immunological response when tetanus toxoid is administered subsequently (Eckmann, 1963) and such self-produced antibodies are naturally superior to heterologous or even homologous antitoxin.

Diazepam and tetanus toxoid are the only two additional therapeutic agents used in Singapore in recent years in the treatment of tetanus cases (Gwee, 1968), and it might be argued that our low mortality rate could be ascribed to one just as well as to the other or even to a combination of both. Undoubtedly there have been several publications showing that diazepam is equal if not superior to the older sedatives and anticonvulsants like barbiturates and chlorpromazine(Bern, 1966; Femi-Pearce, 1966; Hendrickse and Sherman, 1966). However, we are somewhat dubouis that diazepam was responsible for the improved mortality as our dosage was very conservative except in one case.

Confining ourselves strictly to our own cases we are consequently inclined to give most of the credit to tetanus toxoid.

However, our enthusiasm for it is somewhat dampened on examining the records of all tetanus cases admitted to the General Hospital in 1967. We found a total of 36 cases which came from the three Medical Units, the two Paediatric Units catering for patients under 10 years of age, and the Orthopaedic Department. Out of the 36 cases there were 10 deaths, giving a mortality rate of 28%.

9 cases were from the Paediatric Units with 5 deaths, but as these cases would include neonatal tetanus which has a notoriously high fatality rate, they were excluded from comparison with our series. The single case from the Orthopaedic Department survived.

There were 12 cases from Medical Unit I with 4 deaths, and the breakdown in terms of age, site of infection, incubation period, presence of generalised spasms and outcome is shown in Table II.

TABLE I

Med. Unit III Case	Age	Site of Infection	Incubation Period	Period of Onset	Highest T. within first 24 hours	Reflex Spasms	Grade of Severity	Grade according to Patel & Joag (1959)	Result
1.	44	Foot	10 days	48 hrs.	102°F	Frequent	Severe	4	Died
2.	13	Foot	5 days	24 hrs.	100°F	Infrequent	Moderate	5	Recovered
3.	13	Middle ear	? 24 hrs.	3 days	100°F	Frequent	Severe	4	Recovered
4.	14	Unknown	Unknown	12 hrs.	99.2°F	Infrequent	Moderate	4	Recovered
5.	14	Foot	Unknown	—	99.2°F	None	Mild	2	Recovered
6.	14	Neck	2 days	—	98.4°F	None	Mild	2	Recovered
7.	36	Elbow	4 days	5 days	98.4°F	Frequent	Severe	3	Recovered
8.	43	? Teeth	Unknown	—	98°F	None	Mild	1	Recovered
9.	15	Foot	8 days	< 48 hrs.	99°F	Frequent	Severe	4	Died
10.	68	Foot	3 weeks	—	98°F	None	Mild	1	Recovered
11.	37	Foot	8 days	3 days	98.4°F	Infrequent	Moderate	2	Recovered
12.	12	Foot	? 14 days	48 hrs.	98°F	Frequent	Severe	3	Recovered
13.	14	Foot	8 days	48 hrs.	101.8°F	Infrequent	Moderate	4	Recovered
14.	40	Foot	7 days	—	97.6°F	None	Mild	2	Recovered
15.	57	Hand	4 days	7 days	98.4°F	Infrequent	Moderate	3	Recovered
16.	12	Foot	11 days	48 hrs.	100.3°F	Frequent	Severe	4	Recovered
17.	40	Uterus	11 days	—	100°F	None	Mild	2	Recovered
18.	33	? Teeth	Unknown	—	100°F	None	Mild	2	Recovered

TABLE II

Med. Unit I Case	Age	Site of Infection	Incubation Period	Reflex Spasms	Result
1.	40	Foot	5 days	Absent	Recovered
2.	48	Unknown	10 days	Present	Recovered
3.	32	Unknown	10 days	Absent	Recovered
4.	34	Foot	15 days	Absent	Recovered
5.	25	Foot	1 week	Present	Recovered
6.	13	Foot	1 week	Present	Recovered
7.	59	Foot	1 week	Absent	Recovered
8.	41	Leg	9 days	Absent	Recovered
9.	67	Ear	2 weeks	Absent	Died
10.	12	Unknown	Unknown	Present	Died
11.	43	Unknown	Unknown	Present	Died
12.	40	Leg	Unknown	Absent	Died
Med. Unit II Case					
1.	58	Foot	1 week	Absent	Died
2.	18	Unknown	Unknown	Absent	Recovered
3.	26	Foot	1 week	Absent	Recovered
4.	23	? Chest	3 weeks	Absent	Recovered
5.	13	Knee	8 days	Absent	Recovered
6.	34	Unknown	Unknown	Present	Recovered
7.	25	Teeth	12 days	Absent	Recovered
8.	21	Foot	2 days	Absent	Recovered

Medical Unit II had 8 cases with 1 death, and the breakdown likewise is shown in Table II.

The remaining 6 cases (cases 11-16 in Table I) were from Medical Unit III with no mortality.

Thus the combined mortality rate for cases from Medical Units I and II was 25%, compared with 0% for Medical Unit III in 1967 and 11·1% for our entire series of 18. As Medical Units I and II did not participate in our prospective study, their case-notes were not sufficiently detailed to allow exact grading of their patients or strict comparison with our series, but generally speaking they were certainly less severe than ours.

The disquieting point is that the cases from Medical Units I and II were treated along broadly similar lines to ours. Tetanus toxoid and antitoxin were given to the vast majority of cases at entry, including the 5 fatal cases. 2 of these 5 cases were not given diazepam. However, it is consoling to note that even in their figures, the mortality rate of 25% represented an improvement on their previous results reported locally.

Thus taking the overall picture, our success in the treatment of tetanus could be due to more than one factor: tetanus toxoid is probably beneficial, and diazepam may be superior to

the older sedatives and anticonvulsants, and finally the importance of intensive care provided by the medical and nursing staff must play an important part.

A note of caution is necessary in that from the last quarter of 1966, it has been a routine to give all cases of injury coming for casuality treatment an injection of tetanus toxoid with instructions to come back for one more injection at a specified period if they had no previous active immunisation, these instructions being usually ignored. It has been found that most of the local patients are unable to say definitely whether they have been immunised. Hence it is not impossible that a number of tetanus cases in 1967 might have had at least a dose of toxoid previously, for by the end of that year at least 30,000 cases had received one dose of toxoid in the casuality department and this might have contributed to an overall fall in mortality rates. However, direct questioning of the cases of tetanus has failed to adduce any evidence to support the above possibility, and it is probable that the benefit arising from such an event is negligible when all the cases are taken as a whole.

SUMMARY

18 consecutive cases of tetanus were seen in Medical Unit III over a period of 2 years between 1966 and 1968.

Conventional therapeutic methods were employed, these being intensive nursing care, sedation and anticonvulsant therapy with phenobarbitone, chlorpromazine and diazepam, antibiotics and antitoxin, and if necessary surgical treatment of the site of infection, tracheostomy, curarisation and intermittent positive pressure respiration.

In addition every patient on admission was given tetanus toxoid, which is rarely employed in this way. There are theoretical grounds for such use and it is believed that it might have contributed to our gratifying therapeutic results, our fatality rate in Medical Unit III being 11·1%.

However the less favourable experiences in Medical Units I and II would suggest that other factors like intensive care resulting from special interest in the disease and the use of diazepam might have been of similar importance in our success.

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REFERENCES

1. Abel, J.J. et al. (1935): "Researches on tetanus," Bull. Johns Hopk. Hosp., 56, 84.
2. Ibid. (1935): 56, 317.
3. Ibid. (1935): 57, 343.
4. Ibid. (1936): 59, 307.
5. Ibid. (1938): 62, 522.
6. Ibid. (1938): 63, 373.
7. Adams, E.B. et al. (1966): "Usefulness of I.P.P.R. in the treatment of tetanus," Lancet, 2,1176.
8. "Bern, Proceedings of the International Conference on Tetanus. Principles on Tetanus," edited by L. Eckmann, Hans Huber Publishers, Bern & Stuttgart, pp. 37, 67-69, 71-75, 337-340, 455-467, 471-483, 486-487, 501-513, 515-518, 527-545 (1966).
9. Brown, A. et al., (1960): "Value of a large dose of antitoxin in clinical tetanus," Lancet, 2, 227.
10. Diaz-Riviera, R.S. et al., (1951): "Management of tetanus; effect of penicillin on Cl. tetani in vivo," J. Amer. Med. Ass., 1635.
11. Eckmann, L., "Tetanus Prophylaxis and Therapy," Grune & Stratton, New York & London, pp. 77, 88-91 (1963).
12. Edsall, G., (1959): "Specific prophylaxis of tetanus," J. Amer. Med. Ass., 171,417.
13. Femi-Pearse, D., (1966): "Experience with diazepam in tetanus," Brit. Med. J., 2,862-865.
14. Ganedran, A., Unpublished report (1964).
15. Gray, G.C., Dundee, J.W., (1966): Correspondence, Lancet, 2,1359.
16. Gwee, A.L., Nadarajah, I., (1960): "A survey of tetanus in Singapore," Sing. Med. J., 1/2, 161.
17. Gwee, A.L., Lee, Y.K., (1962): "A study of tetanus mortality," Sing. Med. J., 3/4,174.
18. Gwee, A.L., personal communications (1968).
19. Hendrickse, R.G., Sherman, P.M., (1966): "Tetanus in childhood: Report of a therapeutic trial of diazepam," Brit. Med. J., 2, 860.
20. Kloetzel, K., (1963): "Clinical patterns in severe tetanus," J. Amer. Med. Ass., 185, 559.
21. Lancet, (1967): Annotation, 1, 886.
22. Laurence, D.R. et al., (1958): "A clinical trial of chlorpromazine against barbiturates in tetanus," Lancet, 1, 987.
23. Laurence, D.R., Webster, R.A., (1963): "Pathologic physiology, pharmacology & therapeutics of tetanus," Clin. Pharmacol. & Ther., 4, 36.
24. Lucas, A.O. et al., (1965): "A comparison of the value of 500,000 i.u. tetanus antitoxin (horse) with 200,000 i.u. in the treatment of tetanus," Clin. Pharmacol. & Ther., 6, 592.
25. Marie, A., Morax, V., (1902): "Recherches sur l'absorption de la toxine tétanique," Ann. Inst. Pasteur, 16, 818-832.
26. Meyer, H., Ransom, F., (1903): "Researches on tetanus," Proc. Roy. Soc. of Lond., 72, 26.
27. Miller, R.H. Rogers, H., (1935): "Present status of tetanus, with special regard to treatment," J. Amer. Med. Ass., 104, 186.
28. Patel, J.C., Joag, G.C., (1959): "Grading of tetanus to evaluate prognosis," Ind. J. Med. Sci., 13, 834.
29. Rose, H.M., Cecil-Loeb Textbook of Medicine, W.B. Saunders Co., Philadelphia & London, 11th ed., p. 229 (1963).

30. Saxena, O. et al., (1966): "Some observations on mortality in tetanus," J. Indian Med. Ass., 47, 227.
31. Scheibel, I., (1955): "The uses and results of active tetanus immunization," Bull. Wld. Hlth. Org., 13, 381.
32. Trinca, J.C., (1965): "Active immunization against tetanus: the need for a single all-purpose toxoid," Med. J. Aust., 2, 76.
33. Vaishnava, H. et al., (1966): "A controlled trial of antiserum in the treatment of tetanus," Lancet, 2, 1371.
34. Vakil, B.J. et al., (1963): "A comparison of the value of 200,000 i.u. tetanus antitoxin with 50,000 i.u. in the treatment of tetanus", Clin. Pharmacol. & Ther., 4, 182.
35. Ibid. (1964): "A comparison of the value of 200,000 i.u. tetanus antitoxin (horse) with 20,000 i.u. in the treatment of tetanus," 5, 695.
36. Van Heyningen, W.E., (1959): "The fixation of tetanus toxin by nervous tissue/Chemical assay of the tetanus toxin receptor in nervous tissue," J. Gen. Microbiol., 20, 291-320.
37. Ibid. (1961): "The fixation of tetanus toxin by gangliosides," 24,107-119.
38. Wilkinson, J.L., (1961): "Neonatal tetanus in Sierra Leone," Brit. Med. J., 1,1721.