LEVEL II (12)

AD

TRANSLATION NO.: (14) USAMRIID-MUL-0562

(11) 10 Jul 78

(12) 23p

TITLE: (6) On the problem of the use of homologous tetanus antitoxins in the treatment of severe tetanus

AUTHOR(S): (10) W. Auerswald, P. Prucke, R. Kucker, F. Marsoner, Hedwig Muller, ~~Helga Seidl~~, K. Steinbereithner and ~~Erika Wagner~~

REFERENCE: Wein Med Wochenschr. 116:229-235, 1966

DISTRIBUTION STATEMENT

Approved for public release;
distribution unlimited

U. S. ARMY MEDICAL RESEARCH INSTITUTE OF INFECTIOUS DISEASES

Fort Detrick, Frederick, Maryland 21701

SECURITY CLASSIFICATION OF THIS PAGE *(When Data Entered)*

REPORT DOCUMENTATION PAGE		READ INSTRUCTIONS BEFORE COMPLETING FORM
1. REPORT NUMBER	2. GOVT ACCESSION NO.	3. RECIPIENT'S CATALOG NUMBER
4. TITLE *(and Subtitle)* On the problem of the use of homologous tetanus antitoxins in the treatment of severe tetanus		5. TYPE OF REPORT & PERIOD COVERED Translation 6. PERFORMING ORG. REPORT NUMBER MUL 0562
7. AUTHOR(s) W. Auerswald, P. Brucke, R. Kucker, F. Marsoner, Hedwig Muller, Helga Seidl, K. Steinbrerithner and Erika Wagner		8. CONTRACT OR GRANT NUMBER(s)
9. PERFORMING ORGANIZATION NAME AND ADDRESS Wien Med Wochenschr 116:229-235, 1966		10. PROGRAM ELEMENT, PROJECT, TASK AREA & WORK UNIT NUMBERS
11. CONTROLLING OFFICE NAME AND ADDRESS USAMRIID Library, Ft. Detrick, Md.		12. REPORT DATE 10 July 1978 13. NUMBER OF PAGES 21
14. MONITORING AGENCY NAME & ADDRESS*(if different from Controlling Office)*		15. SECURITY CLASS. *(of this report)* 15a. DECLASSIFICATION/DOWNGRADING SCHEDULE

16. DISTRIBUTION STATEMENT *(of this Report)*

Approved for public release: distribution unlimited.

17. DISTRIBUTION STATEMENT *(of the abstract entered in Block 20, if different from Report)*

18. SUPPLEMENTARY NOTES

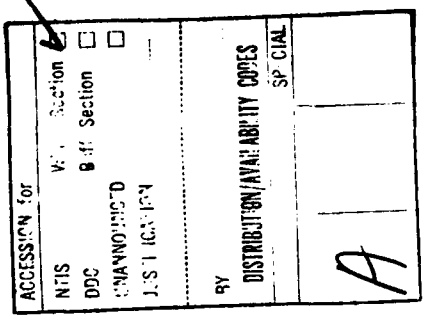
19. KEY WORDS *(Continue on reverse side if necessary and identify by block number)*

Tetanus
Antitoxin tetanus
Homologous tetanus antitoxins

20. ABSTRACT *(Continue on reverse side if necessary and identify by block number)*

DD FORM 1 JAN 73 1473 EDITION OF 1 NOV 65 IS OBSOLETE

SECURITY CLASSIFICATION OF THIS PAGE *(When Data Entered)*



From the Intensive Care Ward of the University of Vienna,

First Surgical Clinic,

Chief: Prof. P. Fuchsig

University of Vienna, Physiological Institute,

Chief: Prof. G. Schubert,

Vienna Federal Institute of Serum Analysis,

Director: Dr. F. Meisl, and

the Institute for Anesthesiology, University of Vienna,

Chief: Prof. O. Mayrhofer

On the problem of the use of homologous tetanus antitoxins in the treatment of severe tetanus

Clinical and immunological observations after therapeutic administration of human tetanus hyperimmune globulin

by W. Auerswald, P. Brücke, R. Kucker, F. Marsoner, Hedwig Müller, Helga Seidl, K. Steinbereithner, and Erika Wagner

Wien Med Wochenschr 116:229-235, 1966

So far, all experiments with etiological therapy for tetanus have failed. Successful operations of recent times concentrated on prophylaxis, which was primarily directed towards obtaining an active immunization of the entire population in a most comprehensive manner.

Even though some objections have been raised about simultaneous immunization, it remains the preferred method used after injury. The objections mostly refer to the insufficient protection during the interval between the fading of the passive immunization's and the onset of the active immunization's effectiveness. Furthermore, it is feared that the effects of antitoxin and of toxoid are reciprocally impaired. However, on the whole this result can be prevented by separately administering a small antitoxin dosage as well as by using adsorbate toxoids.

For an infection diagnosed as tetanus, active rapid immunization with additional administration of tetanus antitixon (TAT) is suggested.

Recently, however, skepticism has been growing against the use of heterologous TAT. Equine TAT, the foreign protein mostly used up to now, causes a sensitization of the patient against the animal protein and may lead to a serum disease as well as anaphylactic shock with its dangerous side effects. (Maurer [17]). If a patient had previously been given TAT, administering the same TAT acts as a booster;

and the antitoxin is eliminated so rapidly through a too sudden development of antibodies against the animal protein of the TAT, that an effective antibody level disappears within days. Besides the shock symptoms mentioned above, the antigen-antibody reactions which appear after the use of heterologous TAT may lead to life-endangering neurological complications, such as encephalitis and polyneuritis with subsequent permanent paralysis. When using heterologous TAT, the frequency of the complications is, reported to be between 5 and 7% on the whole (Summary Voss et. al. [29]). Finally, a certain reservation against the use of increased doses of heterologous TAT exists because the phenol which has been added to some antitetanic preparations as preservative may injure parenchymatous organs. This became evident in some cases of fatal renal insufficiency (Maurath et al.[16], Voss et al. [29]). Therefore, at the International Congress on Tetanus in Bombay it was requested that the use of heterologous TAT be discontinued completely, especially since the disease is not aggravated after abandonment according to extensive Indian statistics (Shah, survey at Mayrhofer et al.[18]).

In view of the disadvantages mentioned above, which speak against the use of heterologous TAT, and of several

indications taken from animal tests which apparently do not allow us to exclude a certain effect on the disease by TAT (Weisschedel [31], Bedjanic and Banic [7], Webster and Laurence [30]), it was logical to use homologous TAT as suggested by Stafford et al. [28] as early as 1954. As a human protein, human TAT does not have an antigenic effect, so that the risks of allergic reactions are eliminated. Preservatives and stabilizers which are contained in TAT-containing gamma globulin preparations are harmless even when large quantities are given. Research on the breakdown rate of human TAT in the organism of healthy subjects (Smolens et al. [27], Rubbo and Suri [23], Rubinstein [24]) revealed its superiority to equine TAT: it showed a half-life of 3 and 4 weeks.

Soldiers who had been vaccinated against tetanus were used as blood donors in 1962 when Neumann [19] described for the first time the application of blood transfusions in tetanus therapy; severe cases of tetanus disease which were treated in this manner were cured.

The first systematic experiment to use TAT-containing human serum in tetanus therapy was made by Ellis [10] in 1963. From 25 patients treated in this manner only two deaths were reported by him. However, Ellis points out that his favorable results are probably due to a lesser degree to the application of human serum but rather to

an increase in experience at his treatment center. Ellis supplied his adult tetanus patients with 20,000 to 80,000 international antitoxin units (AE) and children with 8,000 to 16,000. On the second after the intake of human TAT the serum titer was determined in all patients in the appropriate manner and no values were below 2 AE/ml. The titer was not monitored over some time so that there are no focal points on the rate of disappearance of the antibody in the patient's organism.

Own clinical observations by use of homologous TAT

With respect to the work of Ellis [10] and especially that of Voss et al. [29] and the fact that for some time now, homologous TAT is available in Austria in the form of a tetanus hyperimmune globulin with an antibody concentration of 250 AE/ml, with an addition of Merthiolate as preservative and Glyzine as stabilizer the application of human tetanus hyperimmune globulin was taken into the therapy plan in seven cases of severe tetanus during the last several months. The average dosage amounted to 20,000 AE and was administered intramuscularly. The relatively large volume of 80 ml of gamma globulin was divided into several portions and injected deeply into the intramuscular system. Because of existing reservations against an intravenous application of unmodified gamma globulin (Barandun et al. [6]), the intramuscular form of

injection was selected, especially since the findings of Piringer et al. [20] showed that an even distribution in the plasm and interstitial space is achieved after about two days also with this form of application. In order to obtain information concerning a possible later intravenous administration, a small portion of tetanus hyper immune globulin was infused in two cases intravenously in a heat-inactivated human plasma protein solution, as a 3% solution, in the manner described by Auerswald and Kiesewetter [5], without causing negative side effects. It should be mentioned that in the treatment of the patients before their admission to the hospital equinous TAT and/or tetanus toxoid had been administered in all cases. Therefore, as a matter of routine, administration of this medication was continued, in variying degrees, irrespective of the administration of human TAT. This can also be seen in figure 1.

Table 1 gives a survey of the seven cases treated. It is evident from this that the patients comprise various age groups and that all cases belonged to the tetanus level of severity IV and V. Surgical therapy consisted of excision, and/or amputation: There were no cases with unkown location of entry of the infection so that on the whole the area of infection can be considered to be cured. Tracheotomy was performed on all patients and they were given cava-

catheders (Brücke and Ma. [8], Pokieser and Ma. [21]) for parenteral feeding. The common "lytical mixture" of chlorpromazine, promethazine, and pethidine, and/or dehydrobenzperidol and phentanyl, a mixture which is used in neuroleptanalgesy, further barbiturates and valium (a benzodiasepine derivative). On the suggestion of Seyffert and Wilbrandt [26], all patients were given in addition 25 mg of hydrocortisone in crystal suspension intralumbary, 1 to 3 times during the first two weeks.

Due to limited space, we cannot go into a detailed discussion here on the complications and the course of the disease (see table 1). However, some specific points deserve mention. Negative side effects of the various antitoxins could not be proved in any of the cases with certainty. With the exception of one patient who developed asthma after the spasms subsided and for that reason had to be given continuous artificial respiration while at the same time maintaining the sedation. The agent causing this effect could not be determined. There may be a connection between a patient who died of myocardial infarction and the reaction of the organism to the administration of heterologous TAT. Catalano[9], Roussak[22], and Schaub and Zimmermann[25] believe this to be true.

In respect to the clinical effect of the treatment, it seems that, especially with older patients, a miti-

gation of the disease was achieved. This may be seen in the fact that compared to previous therapy only 2 out of 7 cases required artificial respiration. However, it should be taken into consideration that simultaneously with other measures the patients received hydrocortisone intralumbarly. All of the authors who so far have reported their experiences on this subject, such as Eyrich and Ma. [11] recently, believe that this is a true therapeutic advance even though it is not possible to give specific evidence on the mechanism of the effect (anti-inflamatory effect in tetanus mesodiencephalitis?). Also the above mentioned investigation shows, especially after the first administration, a very noticeable effect of this treatment. It is manifested in a decline of the increased muscular tone and a mitigation of the spasms. On the other hand, when using corticoids it should be taken into consideration that this the formation of endogenous antibodies is inhibited. A massive administration of homologous TAT should not be effected by this. However, the use of heterologous TAT may help weaken negative reactions against the species-foreign protein, while, on the other hand, effect of a toxoid administration which is likely to be expected may be impaired by corticoids.

In none of the above mentioned cases the length of the disease could be shortened with certainty by the use

of human TAT. Ellis [10] comes to the same conclusion. In the case of a young patient the therapy seems to have had no effect at all on the clinical course. Until the 39th day, on which the patient died of pulmonary embolism, spasms could easily be recognized.

The mortality of the disease was not affected. As indicated in the last column of table 1, fatal complications are varied and are not likely to be connected to the TAT therapy, except for the myocardial infarction case which has been discussed above.

Investigation of the behavior of the homologous antibodies administered in the course of the therapy

Except for the orienting significance of the antibody level shortly after the injection of human tetanus serum by Ellis[10], no research has been done on the behavior of homologous TAT in the patient's organism, especially with regard to the dependency of time of the titer drop. There is only detailed information on the antibody level and its drop after administration of prophylactic dosis in healthy test persons (Smolens et al. [27], Rubbo and Suri [23], Rubinstein [24], Greenberg [13]); hereby, half-time of the homologous TAT was set at 3 to 4 weeks and for heterologous TAT at about 4 days. Our previous own research (Auerswald et al. [4], Auerswald and Doleschel [3], Piringer et al. [20]) confirmed that the half-time of

homologous antibodies amounts to at least 3 weeks. Furthermore they showed that the fear that after intramuscular application a significant portion of the antibodies would be broken down and thus be lost (Martin du Pan et al. [15]) is unjustified.

This study tries to find an answer to the question of whether the titers which are to be expected after an intramuscular administration of TAT and based on the above mentioned work, are achieved also in manifested tetanus and whether the half-time values of homologous TAT in the patient vary from those of healthy persons.

The titer analysis in the serum of the patients was performed according to Ibsen's method and the results were recorded in AU/ml [1)]. As mentioned above, the evaluation of the results was made difficult by the fact that already prior to the administration of human TAT, uniformly performed in all cases shortly after admission to the intensive care ward, various amounts of equinous TAT and/or tetanus toxoid had been administered. These medications were completed.

Analogous to previous own research (Auerswald[2]) and following the results of Gitlin et al. [12] with respect to the exchange of gamma globulin between plasma and the extra-

---

1) At this point we would like to express our gratitude to Mrs. Hilde Hartl for her technical cooperation.

vascular interstitial liquid space, the computation of serum titer values to be expected in the normal organism after the intake of a specific amount of antibodies was performed as follows: After reaching the conditions of an equilibrium, that is after about two days, a parenterally supplied antibody class 7S is distributed in the plasma in the amount of 45% and 55% in the remaining extracellular liquid space; the volume of the plasma can be assumed to be about 40 ml/kg of the body weight (Auerswald [1]); in order to calculate the beginning of the theoretical curve of disappearance the requirement for equilibrium should be extrapolated to the time when the injection was given, so that the initial theoretical antibody concentration in the plasma may be calculated based on the equation:

$$\text{AU/ml} = \frac{\text{45\% of the injected antibody quantity in AU}}{\text{plasma volume in ml}}$$

The drop of the curve of disappearance is shown in the half logarithmic system (abszissa = time, ordinate - log AE/ml) as a straight line according to the input half-time which is for the homologous TAT according to our own previous results three weeks and for the heterologous TAT according to Rubinstein [24], four days. Further, it may be assumed that according to the observations by Piringer et al. [20] after an intramuscular supply the effective titer values will reach the theoretical curve of disappearance

Table 1 Composition of the Clinical Course and the Significant Therapeutic Measures

Patient's Sex	Etiology entered into body state, (Land)	Severity	Therapy (surgical)	Artificial respiration	Sedation relaxation	Initial administration of human tetanus hyper immune globulin	course and complications	length of spasms (length of treatment)	result
♂	manure fork big toe, right Lower Austria	III-IV	amputated toe, tracheot. cavacath.	19 days	LM, NLA, barbit. Valium Imbretil	15,000 AU	3 times cardiac arrest, diarrhea, vomiting	24 days (36 days)	Exitus, parench. bleeding lung
♂	excoriatiation, right, knee, Lower Austria	III-IV	excision tracheot. cavacath.	-	barbit. LM, NLA	30,000 AU	hemorrh. diathesis, sept. cava thrombosis, diarrhea, vomiting	39 days (39 days)	Exitus, massive pulmonary embolism
♂	foreign body, right heel, (bone) Burgenland	IV	excision tracheot. cavacath.	-	NLA, LM, barbit.	20,000 AU	absced. pneumonia sept. cava-thrombosis, thrombophlebitis	14 days (47 days)	cured

abbreviations: LM = Lytic mixture NLA = Neuroleptanalgesis

(cont.)

Table 1 (cont.) Composition of the Clinical Course and the Significant Therapeutic Measures

Patient's Sex	Etiology entered into body state, (Land)	Severity	Therapy (surgical)	Artificial respiration	Sedation relaxation	Initial administration of human tetanus hyper immune globulin	course and complications	length of spasms (length of treatment)	result
♀	wood splinter big toe left Burgenland	IV	amput. tracheot. cavacath.	-	LM, NLA barbit.	20,000 AU	diarrhea	19 days (37 days)	cured
♀	wood splinter right thumb Lower Austria	IV-V	excision tracheot. cavacath.	-	LM, NLA, barbit.	20,000 AU	none	20 days (38 days)	cured
♀	wood splinter left thumb Vienna	V	excision tracheot. cavacath.	21 days (because of asthma)	imbretil, Valium, LM, NLA	20,000 AU	once cardiac arrest, elevation of the diaphragm, adipos., possibly pneumon.	10 days (31 days)	Exitus, arrosion bleeding A. anonyma
♂	rusty nail front foot left Vienna	V	amput. tracheot. cavacath.	11 days	imbretil, Valium LM, NLA	20,000 AU	three times cardiac arrest, pneumonia	13 days (13 days)	Exitus anterior-wall infarction

Abbreviations: LM = Lytic mixture NLA = Neuroleptanalgesis

after about two days. Since in the applied titer determination homologous and heterologous TAT cannot be distinguished from each other, the investigation of the theoretical rate of disappearance - when homologous and heterologous TAT appeared simultaneously in the organism - was calculated by forming a sum curve from the separately constructed individual rates of disappearance of both antibodies.

With regard to the applied tetanus hyper immune globulins it was important to exclude that this preparation contain fissural products of the gamma globulin which might pass the kidney filter because of their low molecular weight and thereby cause the titer to drop too fast. A sedimentation analysis of the preparation (ultra centrifuge Spinco model E, analytical rotor D, 52,640 rpm) showed that it concerns a highly purified fraction with the sedimentation constant of 7 S, which merely contains a negligeable additive of a fraction of 10 S but no fractions with sedimentation constants of <7S.

The results of the titer investigations of the seven patients of the above mentioned cases are summarized in figure 1. With the exception of the case illustrated in figure 1b, it is apparent that the titer values of TAT are high during the week following the intramuscular administration of human TAT. With the exception of the patient

P. in figure 1b they do not reach the values of the theoretical sum curve, however, they are close to the hypothetical rate of disappearance of the human TAT. The titers which have been determined at a later time, however, on the whole are very low. To the extent that values were determined 5 to 6 weeks after the injection of homologous TAT, they are about by half a power of ten lower than it would correspond to the theoretical curve of disappearance. In the case illustrated in figure 1 the titer drops very early.

A survey of the entire titer studies confirms the assumption that intramuscularly administered TAT is distributed in a relative short time in the interstitial liquid space in such a manner that a serum titer which approximates to the theoretical expectations is achieved. The established titer values further indicate that Rubinstein's results are correct: the heterologous TAT is eliminated within a few days; this speaks for the extent of the undesired antigen-antibody reactions which occur when using heterologous protein. The fact that the human antibody shows a much steeper drop than observed when it was used prophylactically seems to be very important. This may be caused by the fact that in a manifested tetanus antibodies were bound to free tetanus toxin through binding; in addition, in those cases which repeatedly contained tetanus toxoid antibodies may be connected. As important as the

administration of toxoid as prophylaxis may be upon injury of the patient who has received sufficient basic immunization, on the other hand it is a great problem to administer toxoid in the cases of fiures la, b, and d; apparently these toxoid supplies did not lead to an increase in titer due to the fact that their antigenous effect was neutralized by the administered TAT and at the same time likely causing a loss of titer of the circulating antibody.

Preliminary summary

In contrast to the optimism which is expressed in the report by Voss et al. [29], the above mentioned clinical results are rather modest. However, it should be mentioned that in this case mostly severe cases of tetanus were concerned. The clinical impression of a slight mitigation of the spams and the specific results concerning the behavior of the antibody concentrations in the course of the tetanus therapy, which were done for the first time, may indeed give important clues in the search for an optimum treatment plan of the tetanus disease.

In any event, it may be assumed as a fact that in manifested tetanus it is possible to achieve an initial antibody content in the extra-cellular liquid by use of homologous TAT in the form of a human hyperimmune globulin preparation, which approximates to the theoretical expectations; this occurs about two days after intramuscular

administration. However, the titer drops at a much faster rate in the patient that can be deduced from the biological half-time of homologous gamma globulin.

If TAT is to be used at all in the therapy of tetanus the problem arises whether after outbreak of the disease the antibody may still find an effective use. Research by Webster and Laurence [30] indicate that TAT may only neutralize free tetanus toxin but not the toxin which is connected to the structures of the central nervous system. If, regardless of these facts, one still would like to assume a therapeutical effect of TAT (it may be based on the animal experiments of Weisschedel [31] and/or Bedjanic and Banic [7]) a human antibody should definitely be preferred to an animal antibody. However, an effect may only become possible if the homologous antibody is distributed into the two liquid spaces - plasma and extra-vascular interstitial space - very rapidly and in an initial concentration as high as possible; thus a basis for a competition with the toxin could be established provided it could be achieved in the direction of the central nervous system regardless of the findings of Webster and Laurence [30] and the achievement of very high TAT concentrations which would represent a real therapeutic chance by displacing the fixed toxin.

Setting these conditions requires that initially - if possible after the appearance of the first signs of the

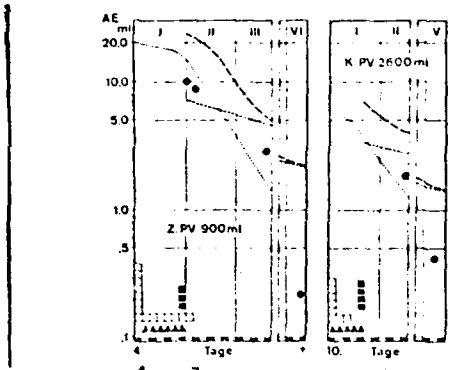
disease - a high dose of no less than 50,000 AE of human TAT is administered whereby about half should be administered intramuscularly and the other half intravenously in order to achieve a rapid flow in of the entire interstitial liquid space of the blood and from the tissue fluid. Based on the above mentioned experience, a further dose of about 5,000 AE should be administered in intervals of about three days in order to prevent the TAT level from dropping. In order to prevent an undesired neutralization of TAT a simultaneous toxoid administration should not be performed.

Only if by use of homologous TAT the conditions mentioned are set - for the continuation of the above mentioned investigation - to specify defined and reproduceable TAT titer in the course of the therapy will it be possible to give a safe opinion on the value of the TAT within the framework of the treatment plan of the tetanus disease. However, until clarification of the question about the therapeutical value of a tetanus antitoxin one will have to follow the previously established suggestions whereby, however, at least as far as human TAT is available, already now heterologous TAT will not be used any longer.

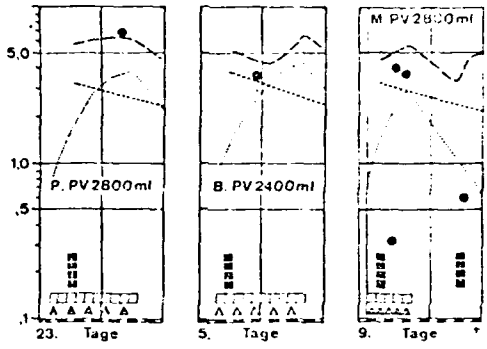
Summary

In 7 cases of severe tetanus (severity grade IV and V) homologous TAT (tetanus antitoxin) was used in the form of

Figure 1: Determination of tetanus antitoxin (TAT) titer in the course of therapy in 7 cases of tetanus.



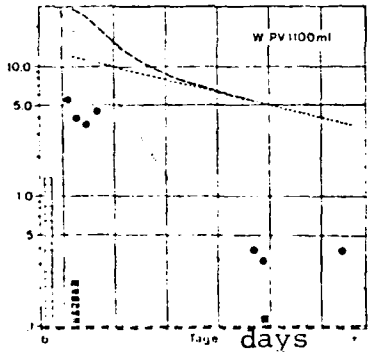
4. days 10. days



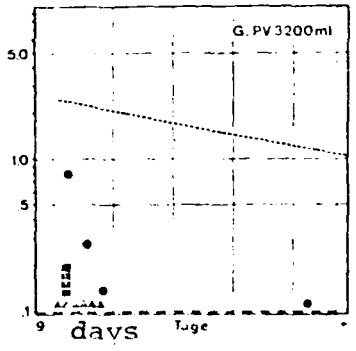
23. days 5. days 9. days

1a: titer curves of two patients who initially were given a high dose of equinal TAT with subsequently small maintenance dosis and daily toxoid injections besides the administration of human TAT.

1b: curves of three patients who were given daily small doses of equinal TAT and toxoid injections in two-day intervals besides human TAT.



days



days

1c: patient, who was initially given a very high dose of equine TAT and then human TAT.

1d: patient, who was daily injected toxoid besides a one-time dose of human TAT.

Abscissa: The days from the time of injury; roman numerals indicate the weeks since admission into the clinic.

Ordinates: TAT titer in the plasma in antitoxin units per ml.

Injections: human TAT = 5,000 AU (20ml of human hyperimmune globulin); equine TAT = 5,000 AU; toxoid adsorbate = 0.5 ml of tetanol

PV: in each instance this is the plasma volume of the patient based on body weight

Titer values: ● actual values determined according to Iben's method.

. . . . . theoretical rate of disappearance of the equine TAT

---------- theoretical rate of disappearance of the human TAT

- - - - - - - sum of the rate of disappearance of both antibodies

---

Summary (cont.)

a human tetanus hyperimmune globulin within the framework of the entire therapy. The administration of equine TAT and/or of tetanus toxoid, part of which was given prior to admission into the clinic and part of it continued after the admission, was followed by administering intramuscularly 20,000 AU of human TAT on the average. Even though the subsequent clinical course of the disease was not shortened, the spasms seemed to migitate slightly. Following the injection, the TAT titer in the patient's serum was monitored over a period of up to 6 weeks and compared with the hypothetical rate of disappearance based on the biological half-time of the antibodies. While the values determined during the first week approximated to this rate of

disappearance, the TAT titer dropped during the further course of the disease much steeper than the theoretical expectations predicted. Within the framework of aiming at interpreting the results, the requirements which are needed for a final evaluation of the therapeutic value of TAT are postulated.

REFERENCES

[1] *W. Auerswald:* Das innere Flüssigkeitsgleichgewicht des Menschen in seiner Abhängigkeit von zentral und peripher angreifenden Faktoren. Wien. Z. Nervenhk. 3 (1950) : 1. — [2] *W. Auerswald:* Bildung, [illegible]rstellung und substituierende Anwendung humaner Antikörper. Wien. klin. Wschr. 73 (1961) : 689. — [3] *W. Auerswald* und *W. Doleschel:* Verteilungsgeschwindigkeit und Verschwinderate intramuskulär zugeführter homologer Antikörper. Wien. med. Wschr. 113 (1963) : 191. — [4] *W. Auerswald, W. Doleschel* und *F. Reinhardt:* Der Übertritt von intramuskulär zugeführtem homologen Gammaglobulin in das Plasmakompartment-Physikochemische und immunologische Untersuchungen an einem Fall von Antikörpermangel. Klin. Wschr. 40 (1962) : 34. — [5] *W. Auerswald* und *E. Kiesewetter:* Untersuchungen über die Verträglichkeit von intravenös zugeführten homologen Antikörpern — Kombinierte Anwendung von Gammaglobulin und hitze-inaktivierter humaner Plasmaproteinlösung. Wien. med. Wschr. 115 (1965) : 690. — [6] *S. Barandun, P. Kistler, F. Jeunet* und *H. Isliker:* Intravenous administration of human gamma globulin. Vox Sang. 7 (1962) : 157. — [7] *M. Bedanič* und *S. Banič:* Bedeutung der Dosierung und Applikationsweise von Tetanusantitoxin bei der Behandlung des Tetanus. Z. Immunitatsf. 125 (1963) : 259. — [8] *P. Brücke, H. Seidl* und *O. Wagner:* Probleme der intravenösen Langzeitinfusion. Klin. Med. (Wien): im Druck. — [9] *Th. C. Catalano:* Myocardial infarction after serum sickness from tetanus antitoxin. J. Amer. med. Ass. 188 (1964) : 1154. — [10] *M. Ellis:* Human antitetanus serum in the treatment of tetanus. Brit. Med. J. 1 (1963) : 1123. — [11] *K. Eyrich, K. L. Scholler, S.* [illegible] *Wiemer* und *H. Noetzel:* Behandlungsergebnisse beim schweren Tetanus. Vortrag gemeins. Tagg. d. Deutschen, Österr. und Schweizer Gesell. f. Anaesthesiologie: 18. 9. 1965 Zürich. Anaesthesist: im Druck. — [12] *D. Gitlin, P. A. M. Gross* und *C. A. Janeway:* The gamma globulins and their clinical significance: I. Chemistry, immunology and metabolism. New Engl. J. Med. 260 (1959) : 21. — [13] *I. Greenberg:* The prophylactic use of tetanus antitoxin. Medical Services J. Canada 19 (1963) : 469. — [14] *J. Ipsen:* Systematische und zufällige Fehlerquellen bei Messung kleiner Antitoxinmengen. I. Mitt. Tetanusantitoxin. Z. Immunitätsf. 102 (1943) : [illegible]. — [15] *R. Martin du Pan, J. J. Scheidegger, P. Wenger, R. Koechli* und *J. Roux:* Das Verhalten der intramuskulär, intravenös und per os verabreichten Gammaglobuline. [illegible] 5 (1959) : 104. — [16] *J. Mannath, E. Kirchner* und *D. Fran*[illegible]*:* Über eine Komplikationsmöglichkeit bei der Behandlung des Tetanus mit hohen Antitoxindosen. Med. Welt (1960) : [illegible]. — [17] *G. Maurer:* Der heutige Stand der Tetanusprophylaxe. Med. Welt (1960) : 157. — [18] *O. Mayrhofer, R. Kucher* und *F. Chott:* Moderne Aspekte in der Tetanusbehandlung. Wien. klin. Wschr. 76 (1964) : 469. — [19] *H. Neumann:* Zur Tetanusbehandlung. Beitrag über die wirksame Unterstützung der Tetanustherapie mit Bluttransfusionen aktiv geimpfter Spender. Chirurg 33 (1962) : 98. — [20] *E. Piringer, W. Auerswald, E. Kiesewetter* und *I. Olegnik:* On the distribution velocity of parenterally administered homologous (human) tetanus antitoxin. Progr. Immunobiol. Standardization 2 (1964) : [illegible]. — [21] *H. Pokieser, K. Steinbereithner* und *O. Wagner:* Zur röntgenologischen Kontrolle von Lage und Funktion des Cavakatheters. Anaesthesist: im Druck. — [22] *N. J. Roussak:* Myocardial infarction during serum sickness. Brit. Heart J. 16 (1954) : 218. — [23] *S. D. Rubbo* und *J. C. Suri:* Passive immunization against tetanus with human immune globulin. Brit. Med. J. 2 (1962) : 79. — [24] *H. M. Rubinstein:* Studies on human tetanus antitoxin. Amer. J. Hygiene 76 (1962) : 276. — [25] *F. Schaub* und *E. Zimmermann:* Coronare Durchblutungsstörung nach Tetanusantitoxininjektion. Z. Unfallmed. 51 (1958) : 238. — [26] *W. Seyffert* und *D. Willbrandt:* Wirksame intralumbale Prednisolonbehandlung des Wundstarrkrampfes. Dtsch. Med. Wschr. 89 (1964) : 1218. — [27] *J. Smolens, A. B. Vogt, M. N. Crawford* und *J. Stokes:* The persistance in the human circulation of horse and human tetanus antitoxins. J. Pediatrics 59 (1961) : 899. — [28] *E. S. Stafford, T. B. Turner* und *L. Goldman:* On the permanence of antitetanus immunization. Ann. Surg. 140 (1954) : 563. — [29] *R. Voss, H. R. Schoen, L. Körner, H. L'Allemand* und *L. Grabow:* Therapie des Tetanus. Münch. med. Wschr. 107 (1965) : 854. — [30] *R. A. Webster* und *D. R. Laurence:* The effect of antitoxin on fixed and free toxin in experimental tetanus. J. Pathol. Bact. 86 (1963) : 413. — [31] *E. Weisschedel:* Die Bindung des Tetanustoxins im Organismus. Arch. klin. Chir. 284 (1956) : 138.

Authors' addresses:

Anschrift der Verfasser: Prof. Dr. W. Auerswald, Physiologisches Institut der Universität, 1090 Wien, Schwarzspanierstraße 17; Dr. P. Brücke, I. Chirurgische Universitätsklinik, 1090 Wien, Alser Straße 4, Doz. Dr. R. Kucher, Dr. F. Marsoner, Dr. Helga Seidl, Doz. Dr. K. Steinbereithner und Dr. Erika Wagner, Institut für Anästhesiologie der Universität, 1090 Wien, Spitalgasse 23; Dr. Hedwig Müller, Bundesstaatliches Serumprüfungsinstitut, 1090 Wien, Kinderspitalgasse 15.