

## SHORT COMMUNICATION

# Tetanus antibody levels of female volunteers after injection with solvent/detergent-treated human tetanus immunoglobulin (Tetabulin S/D)

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## Vox Sanguinis

**Background and Objectives** The aim of this study was to analyse the increase of anti-tetanus titre in volunteers following injection with human tetanus immunoglobulin (HTI).

**Materials and Methods** Twelve females with tetanus antibody titres of  $\leq 0.05$  international units (IU)/ml were injected with 500 IU of human tetanus immunoglobulin (Tetabulin S/D). The tetanus antibody titres were determined before injection, and after 30 h, 48 h and 4 days.

**Results** A fast and sustained increase of protective tetanus antibody levels was observed in 10 of 12 volunteers. No adverse events related to the study drug were reported.

**Conclusions** HTI confers rapid and effective immunity to tetanus.

**Key words:** anti-tetanus titre, immunization, protection, solvent-detergent, Tetabulin S/D, tetanus, volunteers.

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## Introduction

Tetanus has a mortality rate of  $\approx 25$ –50%. Elderly patients are particularly susceptible to the disease [1]. Protection is usually achieved by vaccination with tetanus toxoid [2]. Persons with uncertain immunity may also receive human tetanus immunoglobulin (HTI) for immediate prophylaxis after injury. The only recent study for determination of the increase of anti-tetanus titres after intramuscular (i.m.) administration of HTI was performed by Forrat *et al.* [3]; however, this study included subjects with high antibody levels prior to HTI treatment. The present study analysed antibody titres against tetanus after injection of 500 international units (IU) of HTI in adult volunteers with low tetanus antibody titres.

## Materials and methods

This non-randomized, open-label, non-controlled study was approved by the local Ethics Committee and the Swedish Medical Products Agency. After prescreening for tetanus antibody titres, 12 volunteers with tetanus antibody titres  $\leq 0.05$  IU/ml were injected i.m. with 500 IU of Tetabulin S/D (solvent/detergent-treated HTI) into the gluteal muscle. Tetabulin S/D is manufactured by Baxter AG (Vienna, Austria; the former Immuno AG/Österreichisches Institut für Haemoderivate GesmbH) and is a liquid human polyvalent immunoglobulin concentrate for i.m. use. Tetanus antibody titres were analysed preinjection, and after 30 h, 48 h and 4 days. As low antibody levels are correlated with female gender and increasing age [4], only elderly females were included in the study. The tetanus test had a sensitivity of 0.015 IU/ml and was based on inhibition of the binding of tetanus toxin to an antitoxin-coated immunoassay by tetanus antibodies, according to the Department of Clinical Microbiology at Karolinska Hospital (Stockholm, Sweden) and performed essentially according to Hendriksen *et al.* [5].

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**Table 1** Tetanus antibody titres (in international units [IU]/ml) with descriptive statistics for 12 volunteers

|                         | Pretreatment<br>Day 0 | Time-point after vaccination |           |           |
|-------------------------|-----------------------|------------------------------|-----------|-----------|
|                         |                       | 30 h                         | 48 h      | 4 days    |
| Minimum                 | < 0.015               | < 0.015                      | < 0.015   | < 0.015   |
| Quartile 1              | < 0.015               | 0.03                         | 0.03      | 0.03      |
| Median                  | < 0.015               | 0.06                         | 0.06      | 0.06      |
| CI (95%) for the median | –                     | 0.03–0.06                    | 0.03–0.06 | 0.03–0.12 |
| Quartile 3              | < 0.015               | 0.06                         | 0.06      | 0.09      |
| Maximum                 | 0.03                  | 0.06                         | 0.06      | 0.12      |

## Statistical methods

Quantitative variables were described by medians, quartiles and ranges of values. Medians and non-parametric 95% confidence intervals (CIs) were calculated for the tetanus antibody titres. The number of volunteers (12) included in the pharmacokinetic part of the study was based on the experience of the investigators and ethical aspects, rather than on statistical considerations.

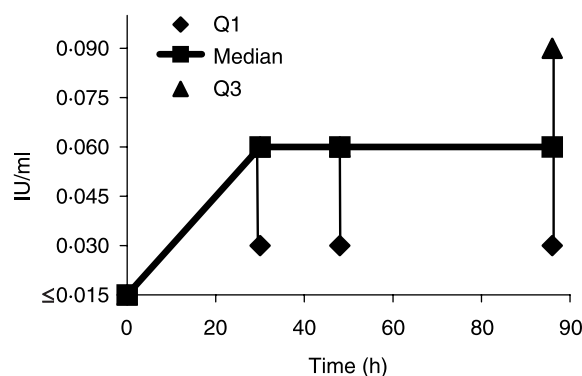
## Results

All 12 volunteers included in this study were females aged 52–72 years and were basically healthy. Tetanus antibody titres after administration of Tetabulin S/D are presented in Table 1 and Fig. 1. Ten of 12 volunteers had a measurable, rapid increase of tetanus antibody titres, which was maintained during the assessment period of 4 days. The median of the tetanus antibody levels on day 4 was 0.06 IU/ml with a 95% CI from 0.03 to 0.12 IU/ml. Tetanus antibody titres at 30 h and 48 h after treatment were the same as or slightly lower than those on day 4 (Table 1).

No adverse events related to the study drug occurred.

## Discussion

Only one of the 12 volunteers had a detectable level of tetanus antibodies prior to treatment. Measurable antibody levels in the range of 0.03–0.06 IU/ml were demonstrated in 10 of 12 volunteers 30 h after injection. These antibody levels were sustained at 48 h after injection. On day 4, three volunteers had a further increase in antibody level from 0.06 to 0.12 IU/ml and one volunteer from 0.03 to 0.06 IU/ml, while the antibody levels were unchanged in the remaining volunteers. Tetanus antibody levels of  $\geq 0.01$  IU/ml are reported to provide protection against tetanus [6]. The reason why two of the females did not respond to immunization remains obscure. Probably, the study drug was injected into fatty tissue, which

**Fig. 1** Tetanus antibody levels (expressed as international units [IU]/ml). Descriptive statistics (Q1, median, Q3) for 12 volunteers.

would have decreased and/or delayed the resorption. It is possible that prolonged observation of the antibody titre would have shown an increase. Scheiermann & Kuwert [7] reported a delayed recovery of immunoglobulins in women compared to that in men. No calculation of plasma volume and recovery was performed. However, as an approximate estimation, a 30% recovery of 500 IU of Tetabulin S/D would result in a tetanus antibody titre of  $\approx 0.05$  IU/ml in an individual with a plasma volume of 3 l. Therefore, the tetanus antibody titres obtained in this study are in agreement with the *in vivo* recovery for intramuscular gammaglobulins, as described by Morell *et al.* [8]. In this study, antibody titre measurements were not performed after 4 days but, according to the known long half-lives of immunoglobulins, sustained, clinically effective levels can be expected.

This study also confirmed the problem with obtaining a correct medical history of previous vaccinations. Thirty per cent of the prescreened volunteers had tetanus antibody titres in the range of 0.5–8 IU/ml, although they denied previous vaccination. From previous studies on tetanus epidemiology [4,9], it follows that elderly patients without documentation of vaccination against tetanus could have a risk of  $\approx 50\%$  of not being adequately protected and should obtain active immunization if they need medical care for wound lesions.

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