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Original Research Aticle

Adverse events following the administration of diphtheria antitoxin (Equine Source): An observational study in an Indian tertiary care centre

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ABSTRACT

Aim: To assess the clinical safety of diphtheria antitoxin in patients with probable and confirmed diphtheria infection.
Materials and Methods: This was a single-center, observational study which included patients with probable and/or confirmed diphtheria infection. The skin sensitivity test for diphtheria antitoxin was performed in all the patients. The patients who were insensitive/ had 'no reaction' to the skin sensitivity test, medically optimal dose of the DAT (10000 IU/10 mL) was administered intravenously.
Results: A total of 203 patients were enrolled in this study, and 200 considered for safety assessments (females, n=104). All patients reported negative skin-sensitivity test. A total of 14 adverse events were reported in six patients (two patients reported three events each while remaining four patients reported two events each) either immediately (75%) or within 5-6 hours (12.5%) of administration of diphtheria antitoxin and therefore, these were considered related to the administration of the drug. These 14 adverse events were non-severe and the patients recovered without sequelae. No further adverse events were observed during the rest of the hospitalization period (4-5 days), after discharge from hospital and during follow-up until 15 days after administration of diphtheria antitoxin. There were no deaths and life-threatening serious adverse events observed.
Conclusion: The observations from the present study suggest that diphtheria antitoxin has a favorable safety profile and it can be essentially used in children as well as adults without any harm.

1. Introduction

Diphtheria is a fatal, transmissible clinical syndrome caused by an exotoxin produced by the bacterium *Corynebacterium diphtheriae*. Even though this is a disease which has been eliminated/controlled in many developed countries and effective vaccines do exist, intermittent cases do occur due to vaccine non-adherence, insufficient booster regimens, and immunosenescence.[1] A resurgence of diphtheria was reported in India in 2018 contributing to 52.8% of reported global cases.[2,3] World-wide, a total of 22,986 cases were reported in 2019, of which 9,622 cases belonged to India.[4]

Rapid administration of Diphtheria antitoxin (DAT) from equine source plus antibiotics is the standard therapy for management of patients with suspected or confirmed diphtheria.[5] It may also be administered to patients with respiratory diphtheria-like illness caused by toxigenic *C. ulcerans*.[6] Passive immunization by DAT is an effective treatment but early treatment is critical, since the extent of protection by DAT is inversely proportional to the interval of diphtheria infection prior to its administration.[7] Until now there is no approved monoclonal antibody to diphtheria

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toxin for clinical use; hence, DAT is the primary treatment for diphtheria and is listed as an essential medicine by World Health Organization.[8] However, restricted production and low market demand has resulted in griming global access to DAT for both therapeutic and diagnostic purposes.[9]

Although, DAT reduces both morbidity and mortality and has well-established efficacy, safety concerns exist with respect to occurrence of hypersensitivity reactions since it is from equine (horse) source. Thus, the present study aimed to assess the clinical safety of DAT in patients with probable and confirmed diphtheria infection at a tertiary care centre from Hyderabad, India. This was achieved by determining the number of the patients experiencing local and/or systemic reactions after DAT administration. Additionally, the incidences of adverse events and serious adverse events occurring during the follow-up period were identified.

2. Materials and Methods

2.1. Study design

This was a single-center, observational study conducted at Sir Ronald Ross Institute of Tropical and Communicable Diseases (SRRITCD) Hospital, Hyderabad, India between January 2018 and May 2019.

2.2. Inclusion and exclusion criteria

The study included all patients presenting clinical symptoms of probable and/or confirmed diphtheria infection, willing to provide consent for inclusion of their medical data and adverse event data in the study and willing to get admitted in the hospital and remain in hospital for about 4-5 days after administration of the DAT, 10000 IU/10 mL, for observation of adverse events of local reactions and systemic nature and other category, if any, by the investigator for safety evaluation, and who provided valid contactable details and willing to be followed-up telephonically after 15-days of administration of the study treatment.

Exclusion criteria used in this study were patients who were likely to discontinue participation from the study without any intimation to the investigator, who tested positive during skin sensitivity test, who were expected to participate in any other clinical trial during the present study period, who had participated in any other clinical trial within the past three months of the present study, or with any other medical condition as per the opinion of the investigator which would have posed a health risk to patient or would have interfered with the result of the present study.

2.3. Study procedure and treatment administration

Eligible patients with suspected and/or probable diphtheria infection were admitted to hospital. The skin sensitivity test for DAT was performed in all patients to identify any hypersensitivity or allergic reaction upon administration of this antitoxin of heterologous nature. For hypersensitivity testing DAT was used as 1:10 dilution and the injection was given on the right forearm intradermally and the induration was noted in 30 mins. If the induration was more than 10 mm DAT was not given. Simultaneously, for confirmation of *Corynebacterium diphtheria* using Klebs Loeffler bacilli (KLB) smear test and culture sensitivity the first throat swab sample was collected at presentation of the patient in the study site. For the patients who were 'insensitive' / had 'no reaction' to the skin sensitivity test, medically optimal dose of the DAT (10000 IU/10 mL) (manufactured by Vins Bioproducts Limited, Hyderabad and supplied by Telangana state government) was administered intravenously by a trained nurse or pharmacist, delegated for the activity in the presence of the investigator and/ or medically qualified personnel from study site, as delegated by investigator. The selected dose of DAT was mixed in 250 to 500 mL of saline and administered as an intravenous infusion over a duration of 2 to 4 hours, with close monitoring for any anaphylaxis. The dose and route of administration of DAT was based on medical judgment of the investigator as per routine care, established as per the severity of the infection and the clinical symptoms presented. The second throat swab sample for confirmation of Corynebacterium diphtheria was collected after 48 hours of collection of the first sample. The patients were observed closely for local reactions and systemic events, if any, both immediately (1-2 hours and 3-4 hours) and within 24 hours of administration of DAT. The occurrence of delayed reactions to the test product was observed during the hospitalization period of about 4-5 days. At the time of discharge from hospital (after about 4-5 days of administration of the antitoxin), the patients were advised to report of adverse events, experienced if any, in their respective 'home-setting'. In all cases of diphtheria, both probable and confirmed, presenting with either mild, or moderate and/ or severe symptoms of the infection, concomitant medication was planned to be prescribed by the Investigator based upon the grade of infection. These medications included antibacterial agents such as ceftriaxone, metronidazole, crystalline penicillin or azithromycin oral in place of penicillin. Other concomitant medications included paracetamol, carnitine and chlorpheniramine tablets, betadine gargling, injection ranitidine, injection hydrocortisone if required in case of bull neck.

2.4. Data collection

The medical data and safety evaluation data were recorded in case record form. The data collected from the patient included sociodemographic factors, chief medical complaints, local examination, immunization status, number of doses of DAT administered, the adverse reactions to DAT, and the concomitant medications used.

The safety evaluation was performed based on the number of adverse events (both serious and non-serious) occurring during or post administration of the diphtheria antitoxin (during 15 days follow-up period).

2.5. Endpoints

Primary endpoints were to determine incidence of early adverse events (local and systemic) occurring immediately at the time of DAT administration, or within 2-4 hours, and up to 24 hours after administration of DAT and incidence of late adverse events occurring within 4-5 days of hospital stay. Secondary endpoint was to examine the incidence of late allergic reactions or adverse events occurring between 5 and 15 days of administration of DAT.

2.6. Statistical analysis

Descriptive analysis was done for demographic data (age and weight) of all the enrolled patients. Quantitative data were summarized as mean and standard deviation (SD) or median and range (minimum, maximum). Qualitative variables were presented as frequencies and percentages.

2.7. Definitions

1. Probable diphtheria infection: An upper respiratory tract illness with an adherent membrane of the tonsil(s), pharynx, larynx or nose that is not laboratory confirmed and is not epidemiologically linked to a laboratory-confirmed case.[10]
2. Confirmed diphtheria infection: An upper respiratory tract illness with an adherent membrane of the tonsil(s), pharynx, larynx or nose, and isolation of toxin-producing *Corynebacterium diphtheriae* from the nose or throat, or epidemiologic linkage to a laboratory-confirmed case of diphtheria or an infection at a non-respiratory anatomical site (e.g., skin, wound, conjunctiva, ear, genital mucosa) with isolation of toxin-producing *Corynebacterium diphtheriae* from that site.[10]

2.8. Ethics

The study was conducted in compliance with Good Clinical Practice guideline and in accordance with the ethical principles that have their origin in the Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects (64^{th} WMA General Assembly, Fortaleza, Brazil, and October 2013). The study protocol was approved by the Institutional Ethics Committee of Osmania Medical College, Hyderabad (IEC/OMC/HYD/2019/65). Written informed consent was obtained from all the adult patients. For patients aged below 18 years, written informed consent was signed by their parents/ guardians.

3. Results

A total of 203 patients were enrolled in this study (females, n=104), and considered for safety assessments, as all patients reported negative skin-sensitivity test. The median (range) age and weight of enrolled patients was 14.0 (2-50) years and 38 (10-105) kg (Table 1). Throat swab culture was positive in 55 patients. During the administration of DAT, due to adverse events, three patients could not be administered with complete dose of DAT (10000 IU/mL). Thus, in total 200 patients completed this study (Figure 1); however, these three patients were followed up and had no further problems and were fine after 15 days.

Table 1: Demographic details of study population

Parameters	Value (N=200)
Median age (range) in years	14 (2-50)
Sex	
Men	96 (48.0)
Women	104 (52)
Median weight (range) in kg	38 (10-105)
Vaccination status	
Given (Fully immunized)	77 (38.5)
Given (Partially immunized)	4 (2.0)
Not given	68 (34.0)
Not known	51 (25.5)
History of allergic reactions	
No	154 (77.0)
Unknown	46 (23.0)
Median (range) duration of complaints in days	3 (1-30)
Number of adverse event-free patients	193 (96.5)
Corynebacterium diphtheriae	
Throat swab culture positive	55 (27.5)

Data presented as n (%) unless otherwise specified.

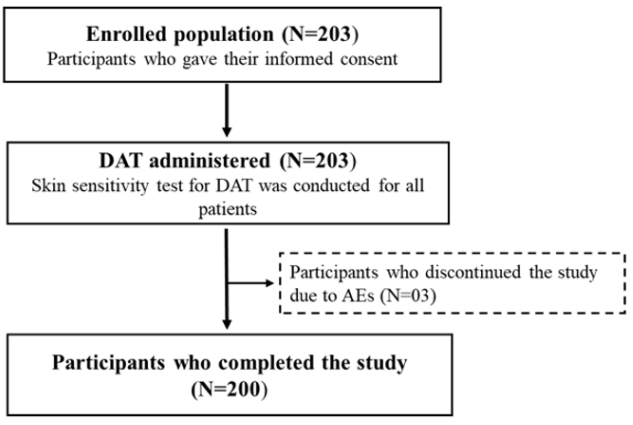

Fig. 1: Disposition of patients
AEs, Adverse events; DAT, diphtheria antitoxin (equine source), 10000 IU/10 mL.

A total of 14 adverse events were reported in total of six patients (two patients reported three events each while remaining four patients reported two events each) either immediately (75%) or within 5-6 hours (12.5%) of administration of DAT and therefore, these were considered related to the administration of the drug (Table 2). These 14 adverse events were non-severe and the patients recovered without sequelae. Among patients who had adverse events two patient had culture positive.

Table 2: Display of adverse events by time of onset after administration of DAT Injection.

Time of Onset	Number of AEs n (%)
Before dosing	02 (12.5)
Immediate	12 (75.0)
Within 5-6 hours	02 (12.5)

No further adverse events were observed during the rest of the hospitalization period (4-5 days) after administration of DAT. There were no adverse events reported by the patients after discharge from hospital followed-up until 15 days after administration of DAT. There were no deaths and life-threatening serious adverse events observed and reported in this observational study. The brief summary of adverse events observed in the patients after administration of DAT is summarized in Table 3.

Adverse events included rashes, edema of lips, shortness of breath, numbness, giddiness, abdominal pain, vomiting, headache, allergic reaction, swelling of face and eye after dosing of DAT. Most commonly used medication to treat these adverse events was pheniramine injection along with hydrocortisone, paracetamol, and ondansetron as and when required. DAT infusion was stopped following the appearance of adverse events and treated symptomatically and once the adverse event subsided, the DAT infusion was continued. More importantly, febrile reactions and serum sickness are not IgE-mediated, therefore are not predicted by skin testing.

4. Discussion

This was a post-marketing surveillance observational study that has assessed the adverse events following the administration of DAT from equine source in patients with diphtheria infection and determined its safety profile. These safety evaluations were performed mainly by determining and assessing incidence and severity of adverse events experienced by the patients after parenteral administration of DAT.

The key observations from the present study demonstrated a favorable safety profile of DAT in patients with diphtheria infection that included a total of 14 adverse events in six patients. These adverse events were non-severe and the patients recovered without further incidence of any other adverse events. Primarily the adverse events occurred immediately in two-third of patients and remaining occurred within 5-6 hours of administration of DAT. No further adverse events/ serious adverse events/ deaths were observed during the rest of the hospitalization period as well as during the 15 days follow-up period after administration of DAT.

Diphtheria continues to be a public health problem in India and reports have shown ten Indian states accounting for most of the reported cases. The median age of diphtheria cases in most of the published studies was ≥ 5 years.[11–15] However, the present study showed the median age of 14 years with patients belonging to a wide range of 2.0-50.0 years of age. This study showed majority of women being infected which is in accordance with reported incidences of diphtheria. Women are more frequently deficient in seroprotection than men posing a high susceptibility risk to diphtheria.[16] Murhekar M in his review article described a higher incidence of diphtheria among females (20 per 100,000) from Hyderabad while in Delhi there was no difference in incidence by gender.[17]

The dose of DAT depends on the duration and the grade of severity of the diphtheria infection. Although, formal clinical trials of DAT administration have not been conducted, the recommended doses of DAT ranges between 20,000 and 120,000 U; but can be administered in larger amounts for patients with vast local lesions and longer duration since onset.[8] Nevertheless, clinicians should be wary about the onset of diphtheria symptoms and prompt administration of DAT in such patients is very critical since it is observed to be ineffective if delayed. Findings from a Latvian study showed that administration of DAT after the second day of symptoms did not exert any beneficial effects in controlling the infection.[18] Administration of DAT on 3-6 days after onset of diphtheria symptoms caused greater severity of diphtheritic polyneuropathy and death whereas when administered on days 1-2 there was no mortality in patients with diphtheritic polyneuropathy.[18]

Administration of DAT is complicated since it is obtained from equine source and hence is accompanied with a risk of acute and delayed hypersensitivity reactions.[19] Patients administered with equine DAT can experience delayed hypersensitivity reactions, such as serum sickness, and infrequently acute anaphylactic shock (5). Injection epinephrine is recommended for acute anaphylaxis.[20]

Patients with the history of asthma, allergic rhinitis, or urticaria are at an increased risk of developing serious anaphylactic reactions upon receiving equine-DAT. Appropriate medical history related to factors causing an increased risk of hypersensitivity reactions should be taken in all the patients receiving DAT. Performing sensitivity test for DAT and careful monitoring during the test is very important. Likewise, patients should be monitored after DAT administration for signs of hypotension and bronchoconstriction. The present study also followed the

Table 3: Summary of adverse events occurred in patients before and after DAT administration

Adverse event	Number of events	Patient details		Dose of DAT injection (IU)	Treatment
		Age (years)	Gender		
Rash	1	7	M	30000	Injection pheniramine
Edema of lips	1				
Shortness of breath	1	25	F	20000	Injection pheniramine, Injection Hydrocortisone
Numbness	1				
Giddiness	1				
Abdominal pain	1	8	M	30000	Paracetamol, Injection pheniramine and Injection ondansetron
Vomiting followed by fever	1				
Headache	1	38	F	65000	Paracetamol
Abdominal pain	1				
Allergic reaction	1	11	F	40000	Injection pheniramine
Swelling on left side of face	1				
Swelling in the left eye	1	16	F	80000	Stopped DAT infusion. Once the adverse event subsided, the DAT infusion was continued
Abdominal pain	1				
Vomiting	1				

F, female; M, male.

same protocol and conducted skin sensitivity test for DAT. All the patients who reported negative skin-sensitivity were enrolled (N=203) and administered DAT.

Anaphylactic reaction, febrile reaction and serum sickness are other possible adverse reactions following administration of DAT. The treatment of an anaphylactic reaction depends on the type and severity of the event. Epinephrine is the standard drug indicated for all types of reactions. Furthermore, medications such as antihistamines, corticosteroids, alpha- and beta-adrenergic blockers are recommended depending on the severity of the reaction. In case fever develops, it generally occurs in 20-60 minutes after exposure to DAT. Febrile reactions are mostly mild that can be treated with antipyretics alone.[21] Angioedema, glomerulonephritis, Guillain-Barré syndrome, peripheral neuritis, or myocarditis are infrequently occurring conditions. The onset of reactions is usually 7-10 days or several hours-3 days after initial exposure to DAT. The present study showed majority of events occurring immediately while few events occurred within 5-6 hours. Dittmann et al. reviewed 1,433 diphtheria cases treated with DAT between 1940 and 1950, reported the frequency of adverse events including anaphylaxis (0.6%), febrile reactions (4.0%) and serum sickness (8.8%).[22] A recently published study from Bangladesh reported that 25% of their study population had at least one adverse reaction which were of mild intensity and the most prevalent adverse reactions included cough (16%), rash (9%), and itching (5%).[23]

Lack of a DAT or inadequate vaccination can increase the likelihood of re-emergence of diphtheria, severe forms of diphtheria and mortality as demonstrated during the shortages in the Newly Independent States and Republic of Uzbekistan diphtheria epidemic.[22,24] Another recent outbreak in Assam, India showed that all the cases were unimmunized or partially immunized emphasizing the need of availability of adequate supplies of DAT for quick medical management of cases.[13] Thus, suggesting the important role of DAT in managing and preventing resurgence of diphtheria outbreaks. Moreover, the incidence and nature of adverse events observed in this observational study suggested DAT to be potentially safe for administration to patients with diphtheria infection in Indian settings.

Considering very few adverse events in this study it may be difficult to analyze and compare these with adverse events in the context of other allergic reactions to equine products. Pyrexia, rash, chills, nausea, and edema are common adverse events reported with Botulism Antitoxin Heptavalent.[25]

4.1. Strengths and limitations of the study

There is limited data pertaining to the safety of DAT in patients with diphtheria infection. Hence, data from this pilot, real-world study in Indian patients provides critical evidence about the safe use of DAT in patients with a wide age group. However, this study is limited by single centre and small sample size. The enrolled patients belonged to the Indian healthcare centres, limiting the strength to generalize these findings over a large population belonging to different geographical locations. Thus, further multi-centric controlled studies are warranted with large cohorts to obtain validated data.

5. Conclusion

In conclusion, the observations from the present study suggest that DAT has a favorable safety profile that can

be essentially used in children as well as adults without any harm. However, vigilant observation of diphtheria symptoms and prompt administration of DAT are the critical aspects of management of diphtheria cases.

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7. Author Contribution

Conceptualization and design, data collection, analysis and interpretation: TSR, KS, and MAK; writing of original draft and supervision: TSR; Critical review and editing: KS and MAK; approval of final draft: TSR, KS, and MAK.

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9. Conflict of Interest

Authors have no conflict of interest to declare.

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