



## Research Article

# Severe cutaneous adverse reactions to Ayurvedic drugs: a ten year study from a tertiary care centre in South India

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## Abstract

**Background:** *Though the system of Ayurveda has traditionally been acclaimed for its safety, questions are being raised by the scientific community regarding the documentation of safety of Ayurveda Medicines. In this article we address cases of severe cutaneous adverse reactions which are possibly related to Ayurvedic drugs.*

**Materials and Methods:** *A ten year retrospective study was carried out where the case sheets of patients admitted in dermatology ward of a tertiary care centre with cutaneous drug reactions were reviewed. Cases with clinical diagnosis of severe cutaneous adverse reactions (SJS, TEN, DRESS or AGEP) along with history of intake of Ayurvedic drugs were collected. Demographic data, clinical data, drug history and blood investigations were recorded. ALDEN scoring was done to determine causality and SCORTEN score in cases of SJS-TEN cases to assess severity.*

**Results:** *Seven out of 179 patients (3.9%) who were admitted with SCAR (4 TEN, 2 SJS and 1 DRESS) had a history of taking Ayurvedic drugs with an ALDEN score of 2-3 implying possible causality. Most were in the 30-40 age group. Female to male ratio was 6:1. Hepatic involvement with elevated liver enzymes and hyperbilirubinemia was the commonest systemic association. Severity of disease based on SCORTEN score in patients with SJS- TEN ranged from 0-4. All the patients were treated with the withdrawal of the culprit drug and administration of systemic steroids and supportive measures. One patient out of the seven, with extensive TEN expired, thus giving a mortality rate of 14.2%*

**Limitations:** *Being severe cutaneous drug reactions, drug rechallenge was not done*

**Conclusion:** *Though rare we may have to consider the potential of Ayurvedic drugs to cause even severe cutaneous adverse reactions. However to ascertain causality and identify culprit agents, collaborative studies with Ayurvedic practitioners are needed.*

**Keywords:** *Severe cutaneous adverse reactions, Ayurvedic drug reactions.*

## Introduction

Severe cutaneous adverse reactions (SCAR) stands for a group of drug reaction patterns that encompass Stevens–Johnson Syndrome (SJS),

Toxic Epidermal Necrolysis (TEN), Acute Generalized Exanthematous Pustulosis (AGEP) and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS).<sup>1</sup> Studies have

revealed that drugs like anticonvulsants, anti tuberculosis drugs, penicillins, cephalosporins, sulfa group of drugs, allopurinol and NSAIDs are more likely to produce SJS-TEN spectrum of illness. DRESS is commonly precipitated by aromatic anticonvulsants, lamotrigine, minocycline, salazopyrine and dapsone. Macrolide antibiotics, hydroxychloroquin, and diltiazem on the other hand are well known to induce AGEP.<sup>2</sup> However studies on Ayurvedic drugs as a cause for severe cutaneous adverse reactions are lacking in literature.

Ayurveda is an ancient Indian system of Medicine being practiced in India since 1500 BC with medications based on complex herbal compounds, minerals and metal substances. The system of Ayurveda always emphasises on safe treatment which includes alleviating the disease by not instigating another disease.<sup>3</sup> However, in practice, and also in Ayurvedic literature, untoward reactions to drugs are encountered but are not clearly addressed. Therefore, implementation of Pharmacovigilance in Ayurveda is the need of the hour to scientifically address this issue.<sup>4</sup>

In this study, the clinical data of patients who have developed severe cutaneous adverse reactions following intake of Ayurvedic drugs have been collected and analysed.

### Materials and Methods

This was a retrospective observational study, extending over 10 years (1<sup>st</sup> January 2005 to December 2014). The study was approved by the Institutional Ethics committee (IEC No. 05/25/2014/MCT) of Government Medical College Trivandrum in and was conducted according to the declaration of Helsinki.

The source of the data were the patient case sheets document repository facility in the Medical Records Library of our institution. These case sheets were clerked earlier by dermatology post graduate students while on ward rounds and supervised by faculty during hospital and clinical training at our institution. A total of 506 case sheets pertaining to cutaneous adverse drug

reactions were utilized to procure the requisite data. Case sheets wherein the clinical diagnosis was SCAR which includes DRESS, SJS, TEN and AGEP as per Regi SCAR group recommendations were considered. Among them, patients who have taken Ayurvedic drugs in the recent past were taken. The data collection form was customized to acquire data regarding ADEs. From each case sheet, patient demographics, past medical and medication history and current medication regimen were collected. In cases where allopathic medications were co-administered, were excluded. Causality assessment using ALDEN score<sup>5</sup> was done and only those 'probable' and 'possible' cases on causality assessment were included in the study. It may be noted that we could not obtain cases of 'very probable', as drug rechallenge was not performed. A detailed proforma containing patients' details including demographic data, drug history, clinical history, past history and co-morbidities were duly filled up. In order to identify the culprit drug, the factors like drug history, temporal correlation with the drug, duration of skin lesions, time interval between the drug intake and onset of rash, morphology of drug eruption, associated mucosal or systemic involvement and improvement of lesions on withdrawal of drug were carefully analysed. In patients receiving multiple drugs, the most likely offending agent was identified on the basis of the type of reaction and the latent period between drug intake and the onset of reaction. This was further confirmed by the history of improvement on the withdrawal of the same. The results of blood and urine investigations, liver function test, renal function test, random blood sugar and in relevant cases, chest X-rays and ultrasound abdomen were recorded. The various subtypes of SCAR manifested in the study population and the associated systemic findings were studied.

### Results

During the ten year study period, 10 out of 179 patients (9.4%) who were admitted in the dermatology department with SCAR with history

of taking Ayurvedic drugs prior to onset of reactions have been selected for the study. Out of the ten, three patients who had also taken allopathic medications, were excluded. Among the remaining seven patients (3.9%), four cases had TEN, two SJS and one DRESS. Females outnumbered the males (female to male ratio was 6:1). The youngest patient was 18 years and the oldest was 75 years, though most were in the 30-40 age group.

The indications for which the Ayurvedic drug was started included improving body weight, headache, jaundice and vaginal discharge. Five patients gave a history of using only a single Ayurvedic drug prior to onset of reaction while two patients had used multiple drugs. Latent period between the drug intake and the onset of symptoms varied from 7 days to 28 days in most patients with SJS- TEN complex while it was 14 days in the patient with DRESS. The drugs prescribed were recorded along with the indication for which it was given and causality was assessed using ALDEN score as shown in Table 1. All cases had an ALDEN score of 2-3 which implies 'possible' causality.

On clinical examination, two patients had pallor and icterus, one patient (DRESS) had lymphadenopathy and five patients had fever and constitutional symptoms. One patient had hepatomegaly and one (DRESS) had hepatosplenomegaly. On routine blood examination, two patients had neutrophilia, two patients had eosinophilia and four patients had a raised ESR. On evaluating organ specific damage, hepatic involvement was encountered in four patients showing elevated liver enzymes with two patients among them showing additional hyperbilirubinemia. Two patients showed an altered renal function and hyponatremia was seen in two patients. Co-morbidities noted in this study population was carcinoma head of pancreas in one patient. Two patients in the study group gave history of drug reactions in the past to certain allopathic medications, but these drugs were not re-administered anytime in the recent past. None

of the patients gave history of cutaneous adverse drug reactions in a close family member.

The severity of disease in all cases of SJS-TEN were ascertained using SCORTEN score,<sup>6</sup> and the duration of hospital stay and final outcome were recorded as in Table 2. All the patients were treated with the withdrawal of the culprit drug and administration of 1-2 mg/kg body weight of prednisolone or betamethasone equivalent, along with supportive measures. The only patient who didn't improve was a 19 year old female who developed TEN following Ayurvedic drug taken for vaginal discharge. She had widespread erosions, developed sepsis, liver derangements, metabolic acidosis and hyponatremia and expired on the 7<sup>th</sup> post-admission day inspite of administering high dose steroids and broad spectrum antibiotics, thus contributing to a mortality rate of 14.2% (1/7) among the patients with SCAR to Ayurvedic drugs in this study group. All other patients had relief of symptoms and were discharged with an average hospital stay of 12 days.

**Table: 1** Causality of SCAR due to Ayurvedic drugs was calculated using ALDEN score.

Ayurvedic drug used	Indication of drug	ALDEN score
Single polyherbal drug	Vaginal discharge	3
Multiple polyherbal drugs	Jaundice	2
Single polyherbal drug	Improving body weight	3
Single polyherbal drug	Headache	3
Single polyherbal drug (Chyavanaprasam)	Improving body weight	2
Single polyherbal drug	Headache	3
Multiple polyherbal drugs	Jaundice	3

**Table: 2** Severity of Drug reaction on SCORTEN evaluation, final outcome and duration of hospital stay

Patient	SCORTEN score	Predicted mortality	Final outcome	Hospital stay
1	3	35.3	Death	17
3	0	3.2	Relieved	6
4	0	3.2	Relieved	5
5	1	3.2	Relieved	8
6	3	35.3	Relieved	23
7	4	58.3	Relieved	14

## Discussion

Although the National Pharmacovigilance Program of India has encouraged reporting of all suspected drug-related adverse events including those caused by herbal/traditional/alternative medicines (Protocol of NPP, Version 1, 2004, p. 17), the number of reports related to ayurvedic/herbal drugs has been emphatically low.<sup>4</sup> Moreover owing to the firmly held belief among Ayurveda practitioners and patients alike, that ayurvedic drugs are safe, accessing data regarding adverse reactions has become a major challenge. Right from obtaining a correct history, recognising the signs and symptoms of a drug reaction, identifying the culprit medicine to proper reporting of adverse drug events, all steps pose as major obstacles.<sup>7</sup>

Herbal treatments are becoming increasingly popular particularly in the field of dermatology. Thus it has become essential for dermatologists to know about their potential adverse effects.

According to Lee et al,<sup>8</sup> virtually all herbal remedies can cause allergic reactions and several can be responsible for photosensitization. Some herbal medicines, contain arsenic or mercury that can produce typical skin lesions as well as systemic complications. Some popular herbal remedies that are known to cause dermatological side-effects include St John's Wort, kava, aloe vera, eucalyptus, camphor, henna and yohimbine.<sup>9</sup>

In a study done on SJS in Indian patients, out of 225 patients with SJS, four patients had Ayurvedic drugs as the causative agent (1.02%).<sup>10</sup>

In our study on patients having SCAR which includes DRESS, SJS, TEN and AGEP, it was found that 10 patients out of 179 patients (9.4%) who presented with SCAR and had Ayurvedic medications prior to development of drug reaction. An ALDEN score was done in all cases to establish causality. Seven patients had an ALDEN score of (2-3) which implies possible causality, so they were included in the study while three patients had a score of 0-1 which implies unlikely causality and therefore were not

considered. So the overall percentage of patients who have developed SCAR which maybe attributable to Ayurvedic drugs among the total patients with SCAR in this study period is 3.4%.

The female to male ratio was 6:1 and this trend of a female preponderance was also seen in a study conducted by Ajanal et al<sup>11</sup>; though only a slightly higher incidence of adverse drug reactions i.e.(1.3:1) was noticed. This may be due to the small study population in our study. The most common age group affected were those of middle age while most Ayurvedic literature categorise the elderly population as the most susceptible group. The reason cited being that females and older age group are believed to have low immunity (*Alpabalayukta*) and more susceptible for drug sensitivity.<sup>12,13</sup>

Causality assessed by ALDEN score revealed a score of 2-3 in all cases which implies 'possible' causality. Furthermore all the formulations in this study comprised of polyherbal formulations with no patients who had taken herbal-biomimetic-formulations known as *Rasaoushadam*, which are implicated in most cases of systemic toxicities.<sup>14</sup> Ayurvedic practitioners vouch on the efficacy and safety of most drugs but also suggest procurement of this herb mix only from reputable sources. Supplements purchased from a non-reputable source or manufacturer may contain additives or toxins which may result in the adverse effects upon consumption.<sup>15</sup>

The most common symptom was pruritus, followed by rash and constitutional symptoms. These findings are similar to the study by Ajanal et al.<sup>11</sup> The most common system affected apart from skin, was the gastrointestinal system, with hepatotoxicity being the most pronounced characterised by the elevated liver enzymes. A major reason for the unsubstantiated lack of incidence of Ayurvedic drug induced hepatotoxicity is the difficulty in proving causality, especially when using multi-ingredient and often unlabelled products and when all other causes of liver disease have not been meticulously ruled out. Nevertheless, medical



providers, particularly gastroenterologists and hepatologists, will attest to the occurrence of hepatotoxicity as part of drug reaction to Ayurvedic drugs as patients seek medical care when they develop severe liver disease.<sup>16</sup>

Regarding mortality as a part of drug reactions to Ayurvedic drugs, a 19 year old female who developed TEN following Ayurvedic drug taken for vaginal discharge had succumbed to sepsis, metabolic acidosis and hepatotoxicity. She had a SCORTEN score of 4 which is associated with a mortality of 48%. Severe disease leading to mortality (4.8%) were reported in a study that was done on traditional Chinese polyherbal medications.<sup>17</sup> Also in a study from south India also showed mortality following drug induced liver injury, especially when drugs contained heavy metals and hepatotoxic volatile organic compounds (hVOCs).<sup>18</sup>

### Limitations

Being severe cutaneous drug reactions, drug rechallenge was not done in any case due to which we could not categorise the drug as 'probable' and 'very probable' on causality scoring. Also due to small number of patients, statistical tests were not done. Content of the polyherbal preparations and whether they were purchased from authentic Ayurvedic sources were not determined.

### Conclusion

It is time to consider the possibility that alternative systems of medicines can have side effects, which can at times be severe. However identifying the culprit agent may prove to be a challenge with Ayurvedic medicines as Ayurveda gives ample scope for the use of medicines based on various factors like *Prakruti, Desha, Kala*, etc.,. So the combination becomes multifold and there is a lack of uniformity from patient to patient and physician to physician. Also, proprietary medicines are also combined with the classical preparations making it further more complicated.<sup>19</sup> Therefore intense efforts in collaboration with Ayurvedic practitioners to ascertain causality and

delineate the culprit agent is absolutely the need of the hour.

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