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Cutaneous Adverse Drug Reactions on application of *Nagaradi Lepa* - A Retrospective analysis

Research Article

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Abstract

Introduction: Cutaneous adverse drug reactions are among the most common types of drug hypersensitivity reactions. Although considered natural and safe, *Ayurveda* medicines can cause adverse reactions. This article highlights the cases of cutaneous adverse drug reactions possibly due to external application of *Nagaradi lepa.* Materials and Methods: This is an observational, retrospective and record based study conducted by analyzing the spontaneous reported ADR forms, caused by the external application of *Nagaradi lepa*, collected over a period of 12 months (April 2022 to March 2023) at Peripheral Pharmacovigilance Centre, VPSV Ayurveda College Kottakkal, Kerala. Results: During the period of one year, 3 cutaneous ADRs were reported due to external application of *Nagaradi lepa.* All the 3 cases fall under the category of Probable according to Naranjo's ADR Probability scale. 2 cases were mild and 1 case was moderate in severity. All the 3 cases were recovered from ADR. Conclusion: Though under reporting, we may have to consider the possibility of Ayurvedic drugs to cause adverse drug reactions. Pharmacovigilance is an ongoing and continuous process. Reporting of ADR to Pharmacovigilance centers help to generate information on ADR related Ayurvedic formulations and also to prevent its recurrence.

Keywords: ADR, Skin rashes, Pharmacovigilance, *Nagaradi choorna,* External applications.

Introduction

Cutaneous adverse drug reactions are the most frequent of all manifestations of drug sensitivity (1). A cutaneous adverse drug reaction is 'any undesirable change in the structure or function of the skin, its appendages or mucous membranes and it encompass all adverse events related to drug eruption, regardless of the aetiology'(2). The incidence of drug induced adverse skin reactions at a dermatology outpatient setting is 2.6% (3). The most common drug groups causing cutaneous ADRs were antimicrobials [45.72%] followed by NSAIDs [18.02%] and antiepileptics [9.66%] (4). Ayurvedic literature contains various references to the occurrence and prevention of drug reactions, however such information is scattered and the compilation and analysis along with the modern concept of drug reactions is a significant need in present times (5). Adverse events reported in relation to herbal products are frequently attributable either to poor quality or to improper use, and it is therefore difficult to distinguish genuine adverse reactions to herbal medicines and herbal products until the cause of such events has been identified (6). There are handfuls of case reports where specific cutaneous adverse effects are documented to be caused by Ayurveda medicines (7, 8, 9).

Till date, the diagnosis of cutaneous adverse drug reactions is purely clinical. Most drug eruptions are reversible and self-limiting on discontinuing the suspected drug (10). ADRs play an important role in assessing drug safety in any system of medicine. Pharmacovigilance plays an important role in optimising drug safety and improving treatment outcomes (11). In general, Pharmacovigilance is the science of collecting, monitoring, assessing and evaluating information from healthcare professionals and consumers on the undesired effects of medications including herbal and traditional drugs (12).

At the Peripheral Pharmacovigilance Centre for ASU & H Drugs at Vaidyaratnam P S Varier Ayurveda College Kottakkal, Kerala, a retrospective hospital-based study was conducted to enumerate the cutaneous adverse events that were documented over a 12-month period (April 2022 to March 2023). The three cutaneous adverse reaction cases that were recorded were after the use of *Nagaradi lepa choorna*. *Nagaradi lepa choorna* (13) is a polyherbal formulation consisting *Vacha* (*Acorus calamus* Linn.), *Nagara* (*Zingiber officinale* Roscoe), *Shallaki* (*Boswellia serrate* Roxb.), *Bola (Commiphora myrrha* (Nees) Engl.), *Laksha* (*Laccifer lacca*), *Chenninayakam* (*Kumari rasa sambhava- Aloe barbedensis* Mill.), *Sarjarasa* (*Vateria indica* Linn.). It is used as an external application in traumatic inflammation and also effective in reducing inflammatory changes in arthritic conditions. The medication was within its safe

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shelf life and was purchased from a GMP certified Ayurveda Pharmacy. The study may provide an insight to the Ayurveda healthcare professionals on the importance of monitoring and reporting ADRs.

Materials and Methods

This is an observational, retrospective, record based study conducted by analysing the spontaneous ADR forms, collected over a period of 12 months (April 2022 to March 2023) at Peripheral Pharmacovigilance Centre for ASU & H Drugs at Vaidyaratnam P S Varier Ayurveda College Kottakkal Kerala. All spontaneously reported Cutaneous adverse reactions caused by the application of *Nagaradi lepa* were evaluated.

The following data were collected from the ADR report.

- **Patient characteristics:** Age, sex, *prakruthi*, diagnosis, preexisting medical conditions were noted.
- **Drug reaction history:** Date and time of initial observation and description of reaction were noted.
- **Drug history:** List of all ASU & H drugs used by the patient during the period of one month preceding the adverse reaction, route of administration, dosage, concomitant use of other drugs including self-medication, whether prescribed or over the counter drug were noted. Past histories of allergies / drug reactions, if any were noted.
- **Details of the suspected drug to cause ADR:** Name, expiry date, any other relevant information associated with drug use like method of administration, whether used under medical supervision or used as a self-medication, dietary precautions, if any were collected.
- **Management of ADR:** The management categories for ADR were abatement of drug, dose reduction, or treatment for ADR
- **Causality assessment:** By Naranjo Algorithm - ADR probability scale as Definite (>9 score), Probable (5-8), Possible (1-4), Doubtful (0 score)
- **Severity assessment:** Classified into mild, moderate and severe with the help of severity assessment criteria developed by Hartwig et al.
- **Outcome assessment:** The patient outcomes were reported as one of the following: fully recovered, not recovered, unknown, and fatal.

Observations & Results

During the period of one year from April 2022 to March 2023, total of 4400 patients were prescribed with *Nagaradi lepa choorna*. Among them, 3 cases were reported with Adverse Events (AE) due to application of *Nagaradi choorna* as *lepam* at PPvC, VPSV Ayurveda College Kottakkal [Table 1]. All of them had itching at the site of the application of *lepa*. Rashes associated with itching seen in case 2 & case 3. None of the patients were suffering from chronic conditions and not taking any other medications. *Dhanyamla* is used to make *lepa* with *Nagaradi choorna* in case 1 and 3, while rice washed water is used in case 2. All the medicines are advised under medical supervision. The ADR is managed only by abatement of suspected drug in case 1 & case 3. Case 2 was treated with *Nyagrodha patra choorna* (14) [leaf powder of *Ficus benghalensis* Linn.] hot sponging, *Bilwadi gulika* (15) 1 twice daily and Vencos gel (16) for external application along with stoppage of drug. The Causality assessment is done using Naranjo's ADR probability scale (17) [Table 2]. The scores of which are 5 (case 1), 5 (case 2) and 6 (case 3). Thus all 3 cases fall under Probable in the scale. The assessment of the severity is done using Hartwig et al criteria (18) [Table 3]. Of them, case 1 and case 3 are mild and case 2 is moderate in severity. All the 3 cases recovered from ADR. In case 1, itching is immediately subsided after washing off the *lepa*. It took 4 days and 1 day for the complete recovery in case 2 and case 3 respectively.

Table 1: Case presentations

	Case 1	**Case 2**	**Case 3**
Age/sex	62/F, OPD	72/M, OPD	46/F, IPD
Prakruthi	*Pitta kapha*	*Vata kapha*	*Vata kapha*
Diagnosis	Cervical spondylosis	OA knee	Low back ache
Pre-existing medical conditions	No	No	No
Date & time of initial observation of reaction	07/01/2023 3.00pm	31/01/2023 10.00am	04/03/2023 11.00am
Description of reaction	Itching at the site of application of *lepa* (back of the neck)	Itching and rashes over the site of application of *lepa* (knee)	Itching and rashes over the site of application of *lepa* (low back)
List of all ASU & H drugs used by the patient during the period of one month	*Vyoshadi kashayam* 90ml BD *Amruthotharam kashayam* 90ml BD *Jadamayadi choornam* as *lepam* *Punarnavadi kashayam* 90ml BD *Amruthotharam kashayam* 90ml BD *Kottamchukkadi choornam* as *lepam*	*Bhadradarvadi kashayam* 90ml BD *Indukantha kshayam* 90ml BD *Pinda tailam* E/A	*Rasnasapthakam kashayam* 90ml BD *Kaishora guggulu* 1 BD *Sudarshana* tab 1 BD *Dhanyamladhara* for 7 days

Concomitant use of other drugs	Not taken	Not taken	Not taken
Past histories of allergies/ drug reactions	No	No	Itching below the breasts since 3-4 months
Details of the suspected drug Name Expiry date Method of preparation *lepa* Medical supervision/ self-medication	*Nagaradi choornam* May 2024 *Nagaradi choornam* mixed with *dhanyamlam* Medical supervision	*Nagaradi choornam* May 2024 *Nagaradi choornam* cooked with rice washed water to get paste like consistency Medical supervision	*Nagaradi choornam* October 2024 *Nagaradi choornam* mixed with *dhanyamlam* Medical supervision
Management of ADR	Drug stopped	Drug stopped + *Nyagrodha patra choorna* for hot sponging, *Vilwadi gulika* 1 Bd, Vencos gel for E/A are advised	Drug stopped
Causality assessment	Score is 5 (Probable)*	Score is 5 (Probable)*	Score is 6 (Probable)*
Severity assessment	Mild	Moderate	Mild
Outcome assessment	Recovered	Recovered	Recovered
***Refer Table 3**			

Table 2: Naranjo Algorithm- ADR probability scale – items and score

Question	Yes	No	Don't know
Are there previous conclusion reports on this reaction?	1	0	0
Did the adverse event appear after the suspect drug was administered?	2	-1	0
Did the AR improve when the drug was discontinued or a specific antagonist was administered?	1	0	0
Did the AR reappear when drug was readministered?	2	-1	0
Are there alternate causes [other than the drug] that could solely have caused the reaction?	-1	2	0
Did the reaction reappear when a placebo was given?	-1	1	0
Was the drug detected in the blood [or other fluids] in a concentration known to be toxic?	1	0	0
Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	1	0	0
Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	1	0	0
Was the adverse event confirmed by objective evidence?	1	0	0
Scoring for naranjo algorithm: >9 = definite; 5-8 = probable; 1-4 = possible; 0 = doubtful			

Table 3: Naranjo Algorithm- ADR probability scale – items and score for each case

	CASE 1			CASE 2			CASE 3		
Question	**Yes**	**No**	**Don't know**	**Yes**	**No**	**Don't know**	**Yes**	**No**	**Don't know**
Are there previous conclusion reports on this reaction?		0			0			0	
Did the adverse event appear after the suspect drug was administered?	2			2			2		
Did the AR improve when the drug was discontinued or a specific antagonist was administered?	1			1			1		
Did the AR reappear when drug was readministered?			0	2			2		
Are there alternate causes [other than the drug] that could solely have caused the reaction?		2				0			0
Did the reaction reappear when a placebo was given?			0			0			0
Was the drug detected in the blood [or other fluids] in a concentration known to be toxic?			0			0			0

Was the reaction more severe when the dose was increased or less severe when the dose was decreased?			0			0			0
Did the patient have a similar reaction to the same or similar drugs in any previous exposure?		0			0		1		
Was the adverse event confirmed by objective evidence?		0			0			0	
Total Score		**5**			**5**			**6**	

Table 4: Hartwig's severity assessment scale

Level 1	An ADR occurred but required no change in treatment with the suspected drug
Level 2	The ADR required that treatment with the suspected drug be held, discontinued, or otherwise changed. No antidote or other treatment requirement was required. No increase in length of stay (LOS)
Level 3	The ADR required that treatment with the suspected drug be held, discontinued, or otherwise changed. AND/OR An antidote or other treatment was required. No increase in LOS
Level 4	Any level 3 ADR which increases length of stay by at least 1 day. OR The ADR was the reason for the admission
Level 5	Any level 4 ADR which requires intensive medical care
Level 6	The adverse reaction caused permanent harm to the patient
Level 7	The adverse reaction either directly or indirectly led to the death of the patient
ADR: adverse drug reaction; Mild = levels 1 & 2; moderate = levels 3 & 4; severe = levels 5, 6 & 7	

Discussion

Pharmacovigilance is like an observational study which deals with the evaluation and monitoring of safety of medicines and thus helps in identifying risk factors. Large numbers of such studies are carried in modern hospitals. But scattered information is available for the ADR profile of Ayurvedic drugs (19). ADRs are common in clinical practice but these are often missed by the clinician and even if they are recognised they are under-reported, as many physicians are unaware of the clinical importance of reporting ADR's (20). This case series elaborates the incidence of skin rashes on the site of application of *Nagaradi Lepa*. Some of the ingredients of *Nagaradi Choorna* have been reported for their adverse reactions. *Kumari* (Aloe vera) has been reported to produce allergic reactions like redness, burning, stinging sensation and rarely generalised dermatitis in sensitive individuals (21). Furthermore, 2 cases of contact dermatitis due to plaster containing *Myrrha* for treatment of wrist tendonitis have been reported (22). Also, contact dermatitis may be observed by topical administration of *Boswellia serrata* extract (23). The positive dechallenge in the cases shows the temporal relation, which points towards an association between the suspected formulation and the event. Hence, in this case, we believe that the event might have occurred due to sensitivity of some ingredients of the *Nagaradi lepa*. In two instances, dhanyamla was employed for the preparation of the paste, while rice washed water was utilised in the third instance. It remains inconclusive to assert definitively that a specific ingredient or the medium employed in the paste formulation directly precipitated the adverse drug reactions (ADR). The reactions thus observed in the current study can be grouped under Type B adverse drug reactions (24) [Table 5]. Among the three cases 2 patients were assessed as *Vata kapha prakriti* and one as *Pitta kapha*. A direct association between *prakriti* and onset of ADR's cannot be ascertained from this. As it is a compound formulation it is difficult to identify the individual ingredient that caused the ADR's. It may also be due to the idiosyncratic nature of the patients to the particular drug. The reactions subsided with the stoppage of application of *Nagaradi lepa* only in two patients. In one patient along with the abatement of drug, medicines were prescribed to counter the condition. *Bilwadi gulika* is used to combat the poisonous effect. *Nyagrodha patra choorna* [*Ficus benghalensis* Linn.] hot sponging is beneficial in pacifying *Kaphapitta* and reduces burning sensation. Vencos gel helps to restore skin colour. It has antimicrobial and antifungal properties.

Table 5: Classification of Adverse Drug Reactions

Type A	Dose-related reactions	Adverse effects at either normal dose or overdose. Eg. Serotonin syndrome or anticholinergic effects of tricyclics
Type B	Non-dose related reactions	Any exposure is enough to trigger such a reaction. Eg. Allergic or anaphylaxis reactions
Type C	Dose and time-related reactions	Due to dose accumulation, or with prolonged use. Eg. Adrenal suppression with corticosteroids
Type D	Time related reactions	Due to prolonged use in a drug which doesn't tend to accumulate. Eg. Tardive dyskinesia from antipsychotics
Type E	Withdrawal reactions	The undesired effects of ceasing the drug. Eg. Opiate withdrawal
Type F	Unexpected failure of therapy	Where a drug undesirably increases or decreases in efficacy-for example, the increased clearance of a drug by dialysis, or the decreased effect of antibiotics due to resistance

Conclusion

Cutaneous adverse drug reactions are the common and easily identifiable clinical presentation of ADR. Most cutaneous ADRs are mild, self-limited and usually resolve after the suspected drug has been discontinued. Eventhough generally considered safe, external application of Ayurveda medicines also causes ADR's. A culture of understanding and reporting of ADR's even if considered mild should be developed among Ayurveda physicians.

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