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SAFETY REPORTING STUDY OF ANTISCABIETIC DRUGS IN A TERTIARY CARE TEACHING HOSPITAL

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ABSTRACT

Objective: This prospective observational study was carried out to identify the incidence and severity of ADRs of antiscabietic drugs in a tertiary care teaching hospital. **Material & Methods**: A total of 120 patients were enrolled in a study. They were randomly divided into 4 groups. Group A received 5% permethrin & oral placebo, group B was given topical placebo cream & oral ivermectin. Group C received topical 1% gamma benzene hexachloride & oral placebo & group D was given 5% permethrin & oral ivermectin. ADRs were monitored & their severity were assessed by using 'Common Terminology Criteria for Adverse Events'(CTCAE version 4). Naranjo's probability scale was used to know causality relationship. **Results**: Total 4 ADRs were identified in 16 patients. The percentage of ADRs in groups A, B, C & D were 10%, 20%, 6.67% & 16.67% respectively. 75% of ADRs were of mild & 25% of moderate type. There were no severe ADR reported in the study. Skin irritation was the most common (n=7, 43.75%) side effect reported. Two ADRs were definite, one was probable & one was possible. There was no doubtful ADR. **Conclusion**: Incidence of ADRs with antiscabietic drugs was 13.33%. More clinical studies are needed to further explore the statistics of ADRs due to oral & topical antiscabietic drugs.

KEYWORDS: antiscabietic drugs, Adverse drug reaction, CTCAE, naranjo's probability scale.

INTRODUCTION

Scabies is a highly contagious; intensely pruritic dermatosis caused by the mite Sarcoptes scabeie var hominis, an obligate human parasite and is transmitted by close, skin to skin contact. Various treatment modalities have been used but the search for an ideal scabicide is ongoing.

The mainstay of therapy in the present era is topical and includes Benzyl benzoate, Crotamiton, Gamma benzene hexachloride (Lindane) and Permethrin. In addition, oral anti-parasitic agent Ivermectin 200 μg/kg/dose has been found to be an effective scabicidal agent as a single or two dose regimens given at 2 weeks of interval,[1] Lindane is also widely used as an agricultural and industrial pesticide, having a toxic profile on accumulation. The literature reviews suggest- that general practitioners should prescribe this scabicide with increased caution for certain at-risk groups and give adequate warnings regarding potential reports of central nervous system toxicity, convulsions and even death following accidental ingestion, overuse or even a single application of Lindane may be noxious,[2,3] Therefore, there is need of a more effective and safer medication for the prevention and treatment of scabies.

Permethrin cream (5%) was introduced in 1989 as an effective scabicidal agent and seems to be a good substitute for Lindane. Ivermectin is administered orally and has the advantage of being cheaper thus improving the compliance but also having many adverse drug reactions. Research has been attempted to find the best anti-scabies drug focusing on efficacy and safety data.

Considering the above fact, present study is planned to know the comparative safety of Gamma benzene hexachloride (Lindane), Permethrin & Ivermectin as monotherapy and combination therapy on scabies patients in the local population of Bareilly.

METHOD & MATERIAL

The study was conducted at SRMSIMS, Bareilly, U.P, a super-speciality tertiary care teaching hospital. The patients included were of the Primary Health Center-DhoraTanda situated at the periphery of Bareilly, in the department of Pharmacology in association with the department of Dermatology. It was an open labeled,prospective, randomized, comparative, parallel group clinical study and the study was performed after the protocol approval by Institutional Ethical Committee.

All the patients fulfilling inclusion criteria who had attended the outpatient department of the PHC, Dhora-Tanda, Bareilly, U.P were considered for the study from July 2013 to May 2014.

The OPD patients of the Dermatology department was evaluated for the clinical establishment of diagnosed scabies. The patients had followed the proper inclusion & exclusion criteria meant for the study. The sample size finalized for the study was 120. These patients were equally divided in 4 treatment groups i.e 30 patients in each group.

Group-A - Patients had received topical 5%Permethrin cream on day 1 and placebo Vit-B complex on day 1 & 15.

Group-B - Patients had applied topical placebo cream on the first day with oral Ivermectin 200µg/kg/dose on 1st& 15th days.

Group-C - Patients had received topical 1% Gamma benzene hexachloride lotion on day 1 & day 15 with placebo tablet of Vit-B complex.

Group-D - Patients received topical 5%Permethrin cream on day 1 with Oral Ivermectine 200µg/kg/dose & placebo Vit-B complex on day 15.

All patients who visited to the Dermatology department of PHC were reviewed by a clinical pharmacist and those patients who met the study criteria were enrolled. Review was done to identify any new symptoms that were not present prior to the start of the drug therapy. Also worsening of existing symptoms and any change in the laboratory values compared with the baseline values were evaluated to detect an ADR. The outpatients were monitored during their subsequent visits to the outpatient department over a period of four months. The World Health Organization (WHO) definition of an ADR was adopted. Objective findings of ADRs were identified from laboratory reports, whereas subjective markers of ADRs were identified from the reviews & also discussion with the patient and clinicians. Both intensive and spontaneous reporting systems of ADR monitoring were adopted.The overall prevalence of ADRs was determined by taking the ratio of total number of patients who experienced ADRs to the total number of patients included in the study.

RESULTS

A total of 4 ADRs were identified from 16 patients giving an overall incidence rate of 13.33%.

In Group-A 10% patients developed ADRs, in Group-B 20% patients had ADRs, in Group-C 6.67% patients & in Group-D 16.67% patients developed adverse reactions during treatment (Table No.1).

Table -1: Category wise distribution of ADRs

ADRs in 4 treatment groups					
Category of patients	Not developed ADR		Developed ADR		Total
Group A (Permethrin)	27	90%	3	10%	30
Group B (Ivermectin)	24	80%	6	20%	30
Group C (Lindane)	28	93.33%	2	6.67%	30
Group D (Combination Group)	25	83.33%	5	16.67%	30
				Total =	120

Severity of ADR was judged by Common Terminology Criteria for Adverse Events (CTCAE) version 4.0, 2009. According to this criteria 75% ADRs were of mild in nature that included, skin irritation & burning of skin.Other ADRs were of moderate type & included nausea & headache. There was no severe ADR .(Table No.2)

Table – 2: Category wise Severity of ADRs

Treatment groups										
Severity of ADRs	Group A n=30		Group B n=30		Group C n=30		Group D n=30		Total n=120	
	No.	%	No.	%	No.	%	No.	%	No.	%
Mild	3	10%	2	6.67%	2	6.67%	5	16.67%	12	10%
Moderate	0	0	4	13.33%	0	0	0	0	4	3.33%
Severe	0	0	0	0	0	0	0	0	0	0
Lethal	0	0	0	0	0	0	0	0	0	0
Total	3	10%	6	20%	2	6.66%	5	16.67%	16	13.33%

Sex wise distribution of ADRs was seen in various treatment groups (Fig-1). 10.29% of females showed ADRs out of 56.66% females included in the study whereas this figure was 17.31% in males out of 43.33% included in the study stating more of male preponderance.

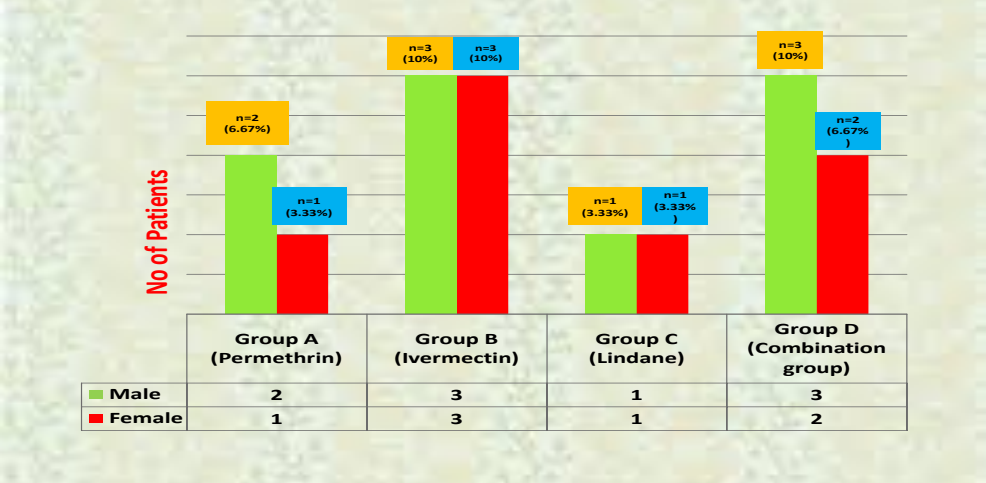

Fig no – 1: Incidence of ADRs according to Sex & Category

Considering, ADRs According to the age range 7.14% patients developed ADRs in between age range 15-20 yrs, 8% patients were in between the age range of 21-35 yrs and 18.75% & 29.17% patients were at the age group of 36-50 yrs and 51-60 yrs respectively , Total 4 ADRs developed under scabies treatment. These are burning sensation, skin irritation, nausea and headache.

In Group-A, 3(10%) patients, in Group-B, 6 (20%)patients, in Group-C, only 2 (6.67%)patients and in Group-D, 5 (16.67%) patients out of 30developed ADRs (Fig- 2).

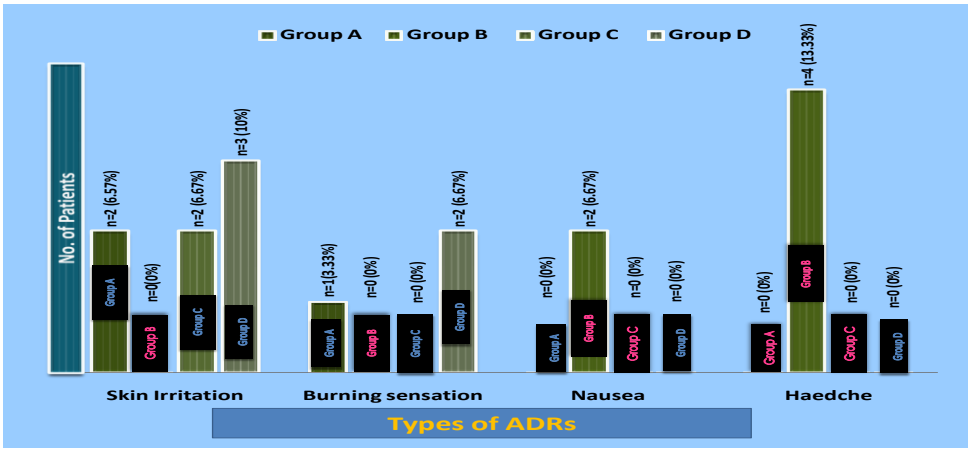

Fig no – 2: Category wise distribution of ADRs

Several criteria has been proposed to increase the objectivity, reliability & validity of causality assessment of ADR. There are two causality categories, Naranjo's Probability Scale (Table No. 3) & WHO-Uppsala Monitoring centre(WHO-UMC)[4] to evaluate validity & clinical usefulness of these criteria. However, there are discrepancies when any ADR is evaluated by these two criteria.[5]

TABLE NO -3: Naranjo 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 re-administered?	+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 ADR; 5–8 = probable ADR; 1–4 = possible ADR; 0 = doubtful

According to Naranjo's Probability Scale in our study, 2 ADRs were definite, 1was probable & 1 was possible. There was no doubtful ADR.(Table No-4)

Table 4: ADR causality relatioship according to Naranjo's Probability scale.

CAUSALITY ASSESSM					
S.No.	**No. of patients**	**ADRs reported**	**Suspected drug/drugs**	**Causality relationship**	**Whether treatment confirmed or stopped**
1.	7	Skin irritation	Permethrin /γBHC	possible	confirmed
2.	3	Burning sensation	Permethrine	probable	confirmed
3.	2	Nausea	Ivermectin	Definite	confirmed
4.	4	Headache	ivermectin	Definite	confirmed

DISCUSSION

In all the 4 treatment groups, no severe/ serious adverse events were observed. Only 3 patients had mild adverse events- mild burning sensation in Permethrin group, headache and

nausea in oral Ivermectin group. Likewise, Group-C had 2 ADRs & Group-D had 5 mild ADRs. All these adverse events subsided without any medication.

Further, Gamma benzene hexachloride has limitations for use in children and pregnant women and there were several reports of central nervous system toxicity, convulsions and even death following accidental ingestion, overuse or even a single application of Gamma benzene hexachloride,[6,7] Therefore, there is a need for a more effective and safer medication for the treatment of scabies in India. [8]

Permethrin cream (5%) was introduced in 1989 for the treatment of scabies and seems to be a good substitute for Gamma benzene hexachloride. It is considered to be the drug of choice in many countries worldwide.[9] but still it is not available in some Asian countries. Hence, we had no estimate about its efficacy and safety in our population. Adverse effects were very rare with Permethrin. Previous comparative studies have showed that Permethrin is also superior to Ivermectin in the treatment of scabies.[10]

Transient burning sensation & irritation of skin was reported by three patients following Permethrin application. While five patients had mild adverse effects in topical Permethrin& oral Ivermectin group like burning sensation, itching, headache. To date, the use of Ivermectine to treat scabies has not been conclusively associated with any serious adverse effects.[11] Oral Ivermectin resulted in headache and nausea in four and two patients respectively that subsided spontaneously without any active intervention.[11]

Two patients in Gamma benzene hexachloride group had stinging sensation over skin. Burning/ stinging sensation was reported in 9.9%, pruritus in 6.4%, erythema in 2.1%, pain in 1.7%, tingling in 0.9% patients by Schultz et al., as side effects of Permethrin,[12] while Chouela et al., reported hypotension, abdominal pain, and vomiting upto 10% of patients with oral Ivermectin.[13] Regarding side effects, Permethrin was found to be significantly safer than Ivermectin ($p<0.05$). Only 3 patients had mild superficial burning as compared to 6 patients in Ivermectin group, like headache and nausea.

Permethrin is known to be significantly safer than Ivermectin ($P<0.05$). Ivermectin has been reported to cause rare serious side effects like neurotoxicity, hepatotoxicity which are seen when the drug is used in high doses, such as when it is accidentally ingested. However, in our study, we found it to be safe without significant adverse effects. Haas et al., used Ivermectin

to decrease burden of side effects. Improve disease by increasing compliance of contacts to multiple doses of the drug. They used it at higher doses of 300 µg/kg in 60 patients, regardless of age. No major side effect was observed and treatment was 100% effective.[14]

These observations are useful concerning the safety of drugs in older people who are generally receiving this drug. Severe scabies, scabies with secondary infection, crusted scabies which is more common in immunocompromised patients respond better to combination treatment with oral Ivermectin, topical scabicides therapy like Permethrin. With an increasing number of patients taking immunosuppressive medications, crusted scabies can be expected to increase in prevalence and oral Ivermectin can help provide a safe and effective treatment option in these complicated cases. Oral Ivermectin at the proposed dose of 200 µg/kg was safe and well-tolerated with no major safety issues. Study of 66 in healthy subjects evaluated single oral dose upto 10 times the proposed dose and showed no major safety concerns,[15] Chosidow et al., have recommended that Ivermectin should be routinely used in patients who do not show response to a topical antiscabietic and it may be the appropriate first choice for the elderlypatients with generalized eczema and others who may be unable to tolerate or comply with topical agents.[16]

CONCLUSION

The incidence of ADRs due to antiscabietic drugs was 13.33%. Most common ADR reported was skin irritation possibly by permethrin. This study provides a representative data of ADR profile of antiscabietic drugs likely to be encountered in India.

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