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LATE ONSET ADVERSE DRUG REACTIONS OF STAVUDINE IN COMPARISON WITH ZIDOVUDINE; REASON FOR DISCONTINUATION

Pharmacology

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ABSTRACT

The main objective of study is to compare the adverse drug reactions (ADRs) of Zidovudine and Stavudine containing regimens. It is a prospective observational study conducted in the ART centre of a tertiary care teaching hospital in central India. The data collected were recorded on standard ADR reporting forms. Standard scales were used for assessment of ADRs. In twelve months duration total 263 patients on ART were observed for ADRs. 128 patients on Stavudine based regimen and 135 patients were on Zidovudine based regimen. Total 72 ADRs detected in 68 patients. Incidence of ADRs was more in Zidovudine based regimen. Zidovudine associated with early and mild ADRs while Stavudine associated with late and distressing ADRs. Considering the magnitude of ADR related problems, results support the discontinuation of Stavudine based regimens.

KEYWORDS

antiretroviral therapy; adverse drug reaction; HIV; AIDS; WHO

INTRODUCTION

The introduction of highly active antiretroviral therapy (HAART) has led to a significant reduction in AIDS related morbidity and mortality1. As of 2016 approximately 36.7 million people have HIV worldwide2.In India total number of people living with HIV was estimated at 21.17 lakes in 2015. While this may seem low, because India's population is so large, it is third in the world in terms of greatest number of people living with HIV.

Stavudine (d4T) and zidovudine (AZT) belongs to nucleoside reverse transcriptase inhibitor (NRTI) group of drugs and they are the core drugs with lamivudine (3TC) as the first-line therapy. Like most medicines, antiretroviral drugs can cause side effects. These medicines are associated with significant safety concerns including serious ADRs, with both short and long term effects.

Stavudine is one of the anti-retroviral agents used in HAART regimens which have severe late side effects in comparison with the Zidovudine. The use of Stavudine is associated with lactic acidosis/symptomatic hyperlactataemia, lipoatrophy, and peripheral neuropathy3. Despite these serious side effects up to 60% of HIV-positive patients in low and middle income countries are receiving stavudine 4, 5.

Continuous evaluation of the benefit and harm of ART will help to achieve the ultimate goal of making safer and more effective treatment available to patients. The purpose of this study was to assess which of these two medications was the best for people living with HIV at term of long term toxicity.

MATERIALS AND METHODS

Objective

To compare the long term safety of Zidovudine (AZT) + Lamivudine (3TC) with Stavudine (d4T) + 3TC, each in combination with Nevirapine (NVP) according to incidence of Adverse Drug Reactions.

Study design & source population

It was a prospective observational study conducted in the Anti Retroviral Treatment (ART) centre of a tertiary care teaching hospital in central India.

The source population consists of AIDS patient on anti retroviral therapy. HIV-positive cases who were already on ART and who were newly started on ART were included. The patients were grouped based on the two regimens stavudine + lamivudine + nevirapine and zidovudine + lamivudine + nevirapine.

Methodology

Two hundred sixty three cases on antiretroviral treatment (ART) were studied prospectively. 135 cases were on Zidovudine based regimen, and 128 cases were on Stavudine based regimen. Data about adverse drug reactions (ADRs) were collected from case records in ART center and an active search was also used to collect ADRs for the duration of one year.

All relevant information recorded in ADR reporting form obtained from CDSCO website6. Cases were further analyzed for drug regimens associated with ADRs and their causality and severity assessment.

Assessment of causality of ADR done by WHO causality assessment scale7. Modified Hartwig And Seigel Scale was used to assess severity of ADR8 . Assessment of Preventability of ADR done by Modified Shumock and Thorton criteria9.

The research protocol was approved by institutional ethicscommittee.

RESULTS

Baseline characteristics

Table 1 contains the baseline characteristics for patients by treatment group. In the d4T group out of 128 patients, 68(53%) were male and 60(47%) were female. Mean age of patients in group was 33.80±14.12 years and mean weight was 41.95±13.74kg.The mean CD4 T-lymphocyte count was 286.04±249.9.

In the AZT group out of 135 patients, 88(65%) were male and 47(35%) were female. Mean age of patients in group was 38.37±11.55 years and mean weight was 47.92±9.71kg.The mean CD4 T-lymphocyte count was 267±182.5. (Table 1)

Table 1: baseline characteristics of total Patients

Groups	Male	Female	age(years)Mean±SD	weight (K.G.) Mean±SD	CD4 cell count (cells/liter) Mean±SD
Stavudine regimen	68 (53%)	60 (47%)	33.8±14.1	41.9±13.7	286.0±249.9

Zidovudine regimen	88 (65%)	47 (35%)	38.4±11.6	47.9±9.7	267.0±182.5

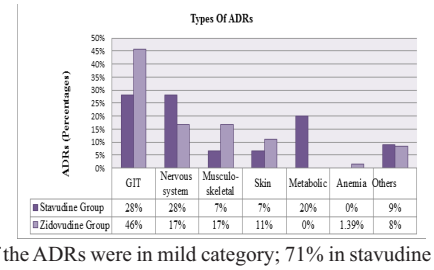
Adverse drug reactions profile:

Out of 128 patients on Stavudine based regimen, 29 had total 45 ADRs; while 39 out of 135 patients on Zidovudine based regimen had total 72 ADRs. Peripheral neuropathy and lipodystrophy were commonest ADRs due to Stavudine based regimen. ADRs related to gastrointestinal tract like nausea and vomiting were commonly presented ADRs in patients on Zidovudine based regimen.
(Table 2 / Figure 1)

Table 2: Types of Adverse drug reactions

Organ System	Types of ADRs	Stavudine group	Zidovudine group	total Number
Gastrointestinal (GIT) 46 (39%)	Nausea	5	14	19
	Vomiting	2	10	12
	Abdominal pain	3	7	10
	Anorexia	3	2	5
Nervous system 25 (21%)	Peripheral Neuropathy	11	0	11
	Headache	1	8	9
	Dizziness/ Vertigo	1	4	5
Musculo-skeletal 15 (13%)	Myalgia	0	8	8
	Arthralgia	1	3	4
	Weakness	2	1	3
Skin and appendages 11 (9%)	Skin Rashes	2	6	8
	Pruritus	0	1	1
	Pigmentation (nail)	1	1	2
Metabolic and nutritional disorders 9 (8%)	Lipodystrophy	5	0	5
	Weight Loss	4	0	4
Red blood cell disorders 1 (0.85%)	Anaemia	0	1	1
Others 10 (9%)	Uneasiness	4	6	10
	TOTAL	45	72	117

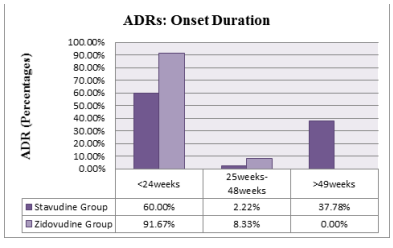
Figure 1: Types of Adverse drug reactions



Most of the ADRs were in mild category; 71% in stavudine group and 79% in zidovudine group.

Figure 2 contains the onset duration of ADRs after starting the ART. In Zidovudine group around 92% and in Stavudine group 60% of ADRs appear within six months of therapy.

Figure 2 : Onset duration of ADRs



Late onset ADRs which appear after 48 weeks of starting the drugs are mainly present in Stavudine group. Around 38% of ADRs in Stavudine group appear after 48 weeks of therapy.

Early Adverse effects

ADRs related to gastrointestinal tract, skin and others like uneasiness were common in first 4 weeks after initiation of ART. These included ADRs like nausea, vomiting, abdominal pain, anorexia, skin rashes and pruritus.

Nervous system related ADRs like vertigo, headache and red blood cell disorders like anaemia were observed within 6-10 weeks of therapy.

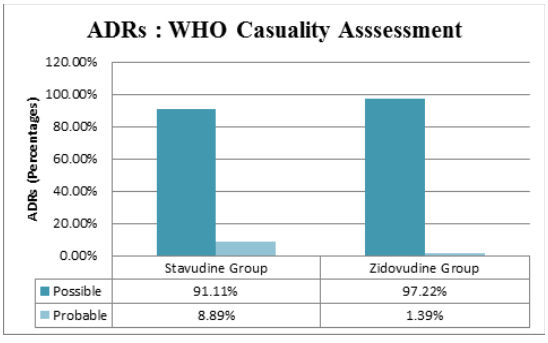
Late Adverse effects

Musculo-skeletal system related side effects like myalgia, Arthralgia and weakness were seen after 24 weeks of ART. Some adverse effects like peripheral neuropathy, lipodystrophy and gynaecomastia were observed after 52-72 weeks of ART.

Causality assessment and Preventability of ADRs

The causality of suspected drug was assessed using WHO scale of ADR causality assessment. The assessment revealed most of ADRs were Possible in both the group. Around 9% ADRs in Stavudine group and 1.4% ADRs in Zidovudine group were Probable. (Figure 3)

Figure 3: WHO Causality Assessment



Preventability of reported ADRs was studied using Modified Shumock and Thorton criteria.64.44% ADRs in Stavudine group and 55.56% ADRs in Zidovudine group were not preventable

DISCUSSION

In our study we compared the ADRs profile of nucleoside analogue combinations Stavudine plus Lamivudine and Zidovudine plus Lamivudine when used in triple combination with Nevirapine. An active search for patients with ADRs was conducted for the duration of one year.

According to WHO recommendations - First-line therapy should consist of an NNRTI + two NRTIs, one of which should be Zidovudine (AZT) or Tenofovir (TDF). Countries should take steps to progressively reduce the use of Stavudine (d4T) in first-line regimens because of its well- recognized toxicities. Alternative options (AZT and TDF) are more expensive, require more laboratory monitoring and have higher initial discontinuation rates10,11. In resource-limited settings, d4T continues to play a critical role in the scaling up of ART, where approximately 56% of HIV regimens still contain d4T12. Cumulative exposure to d4T has the potential to cause disfiguring, painful and life threatening side-effects, such as lipodystrophy, peripheral neuropathy and lactic acidosis13, 14.

Adverse drug reactions profile: Various literature described Limitations of antiretroviral therapies because of adverse reactions. In this analysis a total of 117 adverse events have been reported by 68 patients out of 263 that were studied. In Stavudine group, 29 patients had total 45 ADRs; while 39 patients on Zidovudine based regimen had total 72 ADRs.

Despite the lack of serious toxicity in our study, the frequent mild toxicities do influence a patient's willingness to adhere to a regimen. This may be especially pertinent for the patient who is treatment-naive and otherwise asymptomatic.

The incidence of ADRs was higher in patients with Zidovudine group then stavudine group (29% vs. 23%), but more serious ADR were observed with d4T.

In this study, most commonly presented ADRs were related to GIT system (39%). Various studies shows similar finding15-16.gastrointestinal symptoms such as nausea, vomiting and abdominal pain occurred significantly more frequently in the Zidovudine group (46%). Other ADRs more frequently related to Zidovudine based regimen were myalgia , headache , rashes and arthralgia .

Anaemia was also detected in one patient on Zidovudine based regimen. Most of ADRs related to Zidovudine were presented early during treatment and were generally mild in nature.

The most common adverse drug reaction due to Stavudine was peripheral neuropathy. Blake Max et al study17 reported that incidence of peripheral neuropathy varies from 13-24%. Others studies had reported an incidence of peripheral neuropathy as 10%, 12 %18, 19. From the study by Browne et al., quoted by Cherry et al.20, sensory neuropathy was the dose limiting toxicity of d4T and that the incidence of sensory neuropathy (SN) related to both the dose and duration of d4T.

Metabolic adverse reactions were common in d4T containing regimens21-23.In this study ADRs related to metabolism like Lipodystrophy and weight loss were also common with stavudine based regimen. ADRs related to Stavudine were presented late during treatment. The severity of ADR with d4T needed a change of regimen to AZT. Moreover, d4T requires monitoring for long-term metabolic changes, which may lead to morphologic disfigurements that are particularly distressing to females.

ADRs related to the gastrointestinal system mainly presented in first 2-4 weeks of therapy and these ADRs are mild in nature. Most common ADRs related to Zidovudine group related to GIT (46%).Late onset ADRs which appear after 48 weeks of therapy mainly included Peripheral neuropathy and lactic acidosis. These ADRs were commonly present with Stavudine therapy (28% and 20%respectivly). 64.44% ADRs in Stavudine group and 55.56% ADRs in Zidovudine group were not preventable. Most of the ADRs which were not preventable are late onset ADRs.

CONCLUSION

In our study no unexpected toxicity of either regimen was observed but there was difference presented between the regimens in ADRs profile. Zidovudine based regimen presented with early occurring and mild ADRs while Stavudine related to late, well recognized and distressing toxicities. These results support the discontinuation of Stavudine based regimens advocated by the World Health Organization.

DECLARATIONS

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Conflict of interest: None

Ethical approval: Approved by Institutional Ethics Committee
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