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EVALUATION OF SAFETY OF VARIOUS DRUGS USED IN PERIPHERAL NEUROPATHY IN ELDERLY PATIENTS

Pharmaceutical Science

Vandana Dwivedi MD, Assistant Professor, Department Of Pharmacology, MVASMC Mirzapur, UP

Kanak Lata Dwivedi MD, Assistant Professor, Department Of Pharmacology, HIMS, Barabanki, UP

Arun Raj Pandey* MD, Associate Professor, Department Of Anesthesiology, IMS, BHU, Varanasi, UP *Corresponding Author

Ritesh Kumar Pandey DM, Consultant Cardiology, Chandan Hospital, Lucknow, UP

ABSTRACT

Introduction: In current scenario multiple drugs are used to treat or alleviate the problems related to peripheral neuropathy3. Age related change in drug disposition and drug receptors can influence the plasma concentration and response of drugs. Side effects in elderly are supposed to be different than the younger age group. Till date, majority of drug trials have focused on adult population. We have limited information on safety data of drugs used in neuropathic pain in elderly. **Material & Methods:** Adverse effects were studied with the help of Hartwig and Naranjo scales and analysis were done by suitable statistical designs. **Observation & Results:** Overall, only 7 patients developed side effects with very low scores in Naranjo and Hartwig scales. **Discussion:** Maximum no. of adverse effects were seen with pregabalin and only a single incidence of adverse drug reaction (ADR) was reported with Amitriptyline, gabapentin & duloxetine. All the drugs used in our study were having very less side effects which was easily managed either by withdrawal of the drug or by using antidots (Rarely required). **Conclusion:** These findings can help us make an inference that most of these drugs are very safe with very light side effects which could be managed easily. It will be too premature to conclude that the results obtained in this study can be extrapolated because of the very less and unequal no of cases in each drug group.

KEYWORDS

Adverse drug reaction, Safety, Peripheral Neuropathy

INTRODUCTION

Peripheral neuropathy is damage to or disease affecting nerves, which may impair sensation, movement, gland or organ function or other aspects of health, depending on type of nerve affected. Signs and symptoms of peripheral neuropathy might include, gradual onset of numbness, prickling or tingling in feet and hands which can spread upwards in to leg and arms, Sharp, jabbing, throbbing, freezing or burning pain. It is one of the challenging diagnoses encountered by a clinician with an estimated prevalence of 2-8% in general population[1]. The incidence increases in elderly due to aging of peripheral nervous system and high prevalence of age related systemic disorders like autoimmune diseases, alcoholism, medications, infections, trauma, tumors, diabetes mellitus, lumbar canal stenosis, inherited disorders, vitamin deficiency, bone marrow disorders, endocrinopathies, exposure to poisons, stroke and limb amputation[2]. The physiological and metabolic functioning changes with aging and the effect of drugs also changes with changed pharmacodynamics and pharmacokinetics. In current scenario multiple drugs are used to treat or alleviate the problems related to peripheral neuropathy[3]. Age related change in drug disposition and drug receptors can influence the plasma concentration and response of drugs. Side effects in elderly are supposed to be different than the younger age group. Till date, majority of drug trials have focused on adult population. We have limited information on safety data of drugs used in neuropathic pain in elderly. Considering the magnitude of peripheral neuropathy in geriatric subset and the relative scarcity of pharmacological information of drugs used for this entity, we conducted this study on geriatric patients suffering from peripheral neuropathy. The aim of this study was to analyze how aging and frailty affect safety of pharmacotherapy of peripheral neuropathy in elderly[4,5].

MATERIAL & METHODS

Informed consent of the patient for this observational study was obtained with instruction of consulting physician with assurance of not revealing the identity of patient. Total number of 60 patients of the peripheral neuropathy were studied for the duration of 3 months. Clinical features of peripheral neuropathy were used to establish the diagnosis. The treatment was started according to the need and type of neuropathy and the patient was followed for 3 months, in which at least three visits first visit after, 1st and 3th month were necessary, Pregabalin, Gabapentin, Duloxetine, Methylcobalamine and Amitriptyline were used for the treatment purpose and adverse drug reactions were studied. To see the safety of the drugs NARANJO and HARTWIG Scale were accessed.

Table 1: Naranjo Score

	Questions	Yes	No	Don't know	Total score
1	Are there previous *conclusive* reports on this reaction?	+1	0	0	
2	Did the adverse event occur after the suspected drug was administered?	+2	-1	0	
3	Did the adverse reaction improve when the drug was discontinued or a *specific* antagonist was administered?	+1	0	0	
4	Did the adverse reaction reappear when the drug was readministered?	+2	-1	0	
5	Are there alternative causes (other than the drug) that could have on their own caused the reaction?	-1	+2	0	
6	Did the reaction reappear when a placebo was given?	-1	+1	0	
7	Was the blood detected in the blood (or other fluids) in concentrations known to be toxic?	+1	0	0	
8	Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	
9	Did the patient have a similar reaction to the same or similar drugs in *any* previous exposure?	+1	0	0	
10	Was the adverse event confirmed by any objective evidence?	+1	0	0	

Naranjo criteria classify the probability that an adverse event is related to drug therapy based on a list of weighted questions, which examine factors such as the temporal association of drug administration and event occurrence, alternative causes for the event, drug levels, dose – response relationships and previous patient experience with the medication. The ADR is assigned to a probability category from the total score as follows: definite if the overall score is 9 or greater, probable for a score of 5-8, possible for 1-4 and doubtful if the score is 0. Other criteria which were being used wasHartwig's Severity Assessment scale which includes 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. 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 length of stay. 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. On the basis of this the ADR can be classified as a Mild= level 1 and 2, moderate= level 3 and 4, severe= 5, 6. Apart from this Any other drug which is used for the breakthrough pain was asked to the patient and was noted. Any dropouts were excluded with documentation of reasons. (total 64 cases were registered in which 4 were considered as a dropout because of poor follow-up) Base line investigations like CBC, RFT, LFT, RBS along with specific investigations if required was done. Age > 50 yrs of either sex, accepted co-morbidities, Hypertension, Diabetes mellitus, Cerebro-vascular disease, Peripheral vascular disease, Post menopausal osteoporosis, Osteoarthritis, Malignancy, Patient on Chemotherapy were included. Patients who were excluded were of Age < 50yrs or who declined consent or having Acute serious illness (like MI, Stroke, sepsis, electrolyte disturbances). Statistical Analysis- While accessing the various efficacy scales it was found that there were 3 pairs to analyze. First pair was made with changes in scales from 1st to 2nd visit. Similarly, 2nd and 3rd pair was made in between 2nd-3rd and 1st-3rd visit. Friedmans test was applied for the same with the help of SPSS.

OBSERVATION & RESULTS

Out of 60 registered patients of peripheral neuropathy 42 patients were female which shows the high incidence of disease in females. Mean value of the other parameters were as per the table 1.

Table 1: Demography & Other Parameters

	N	Minimum	Maximum	Mean	Std. Deviation
Age	60	50	85	63.30	8.325
Weight	60	30	110	62.25	13.615
Height	60	145	185	157.25	8.862
SBP	60	94	178	144.08	18.181
DBP	60	70	110	85.43	9.652

Out of 60 patients 7 patients had a history of alcohol intake and 14 patients have given the history of tobacco chewing.

Table 2: Addiction

Addiction	Number	Percentage (%)
Tobacco	14	23.3
Alcohal	7	11.7
No	39	76.7
Total	60	100.0

Among 60 patients, 21 patients received gabapentin, 19 patients received pregabaline, 9 methylcobalamine ,8 Duloxitine,3 amitriptyline.

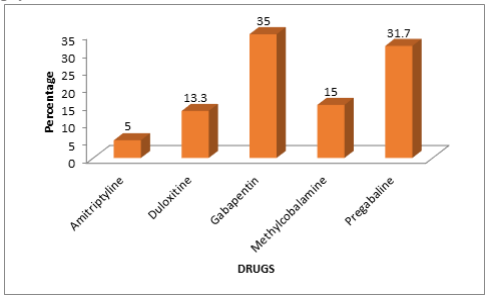

Diagram 1 : Drugs standardization

Table 3: HARTWIG'S And NRANJO'S Scale Scores

NAME OF DRUG	NO. OF PATIENT WITH ADVERSE EVENTS	HARTWIG'S SCORE (Mean)	NARANJO'S SCORE (Mean)
PREGABALINE	4	2	3
AMITRYPTILINE	1	2	3
GABAPENTINE	1	3	4
DULOXETINE	1	3	2

After analyzing the Hartwig's scale it was found that for Pregabalin and Amitriptyline the adverse drug reaction was simply managed with the discontinuation of the respective drugs.

For Gabapentin and Duloxetine, it was found that the ADR was managed with the discontinuation of the respective drug and specific treatment/antidote. After analyzing the Naranjo's scale, it was found that the respective drugs might be the possible reason for adverse drug reactions (1-4, possible reason of ADR)

DISCUSSION

In our study no ADR was seen in methylcobalamine group. Which suggests the good safety profile of the drug which was similar to various other studies showing the good safety and tolerance profile of methylcobalamine in their study[6,7]. Out of 19 cases who received Pregabalin only 4 patients have shown some adverse drug reaction. The mean score was 2 and 3 for HARTWIG and NARANJO scale respectively. Which shows very less severe ADR which can be easily managed with the discontinuation of the drug[8-10]. In various studies it is seen that the incidence of adverse effects, such as sedation (38.50%) and giddiness (36.73%) is less with lower doses[11-13]. Among patients who received Amitriptyline ADR was seen in only one patient. HARTWIG score is 3 and NARANJO scale score is 2 which shows that the drug might be the possible cause of of ADR which can be managed with withdrawal of drug and by giving some other medication for it[14-16]. ADR was seen in only one patient in gabapentin and duloxetine group. There have been a few limitations in our study e.g. This was an observational study, we were not able to include a placebo arm because of logistic reasons c) follow-up of patients was only for 12 weeks and therefore, the long-term efficacy and safety of the study drugs could not be assessed[17-20].

CONCLUSION

Amitriptyline, Duloxetine, Pregabalin, Gabapentin and Methylcobalamine were used for the treatment of peripheral neuropathy in this study. NARANJO & HARTWIG scales were used to access safety, Adverse effect incidence was only 7 in 60 patients which were very mild in nature and were easily managed with discontinuation of the causative drug. Maximum no. of adverse effects was seen with pregabalin and only a single incidence of ADR was reported with Amitriptyline, Duloxetine, Gabapentin. These findings can help us make an inference that most of these drugs are very safe with very light side effects which could be managed easily. It will be too premature to conclude that the results obtained in this study can be extrapolated because of the very less and unequal no of cases in each drug group. More studies with large no of cases and long duration are recommended to perform.

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