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Case Report

Adverse drug reaction due to combination of gabapentin and nortriptyline along with its causality assessment

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ABSTRACT

The combination of gabapentin and nortriptyline is used as the first line drug treatment for management of neuropathic pain; however adverse drug reactions (ADRs) are one of the main causes for discontinuation of the therapy. This is a case study of erythematous maculopapular rash induced by combination of gabapentin and nortriptyline along with its causality assessment. A 55-year-old female came with complaint of back pain for 1 month. She was diagnosed as a case of L1 acute osteoporotic disc compression fracture. The patient was then administered combination tablet of gabapentin and nortriptyline (100 mg/10 mg) orally for the neuropathic pain. After 3 days she developed erythematous maculopapular rash on face, upper limbs and back. Following this the drug was then discontinued and pheniramine, hydrocortisone and combination tablet of levocetirizine and montelukast was administered to treat the rashes. Causality assessment was done using the Naranjo scale and WHO UMC assessment scale. The ADRs was reported by VigiFlow in the pharmacovigilance centre. Causality assessment using Naranjo scale (Score 6) and WHO UMC scale indicates probable relationship. Hence, monitoring is essential for any ADRs while using combination of gabapentin and nortriptyline therapy. In case of ADRs, discontinue the therapy and report the adverse drug reactions to pharmacovigilance centre.

Keywords: Gabapentin, Nortriptyline, Causality assessment, Maculopapular rash

INTRODUCTION

Gabapentin and nortriptyline are the first line drugs for management of neuropathic pain which is the pain caused by damaged/irritated nerves.[1] This is a case study of erythematous maculopapular rash induced by combination of gabapentin with nortriptyline along with its causality assessment.

About 1% to 10% of patients suffer from rash when treated with gabapentin or nortriptyline.[2,3] However, Gabapentin, and its combination with nortriptyline continue to be first line drugs for neuropathic pain. This is because the pain with combination treatment is significantly lower than with gabapentin or nortriptyline alone.[1]

CASE REPORT

A 55-year-old female came with complaint of back pain for 1 month. She was diagnosed as a case of L1 acute osteoporotic disc compression fracture. The patient was then administered a combination tablet of gabapentin and nortriptyline (100 mg/10 mg) orally for the neuropathic pain. Gabapentin is a cyclic GABA analogue that affects voltage sensitive Ca^{2+} channels in neurons. Reduced Ca^{2+} entrance into presynaptic neurons via these channels

lowers glutamate release, reducing neuronal excitability.[4] Nortriptyline is a tricyclic antidepressant which work by inhibiting noradrenaline reuptake.[4] After 3 days she developed erythematous maculopapular rash on face, upper limbs and back. Following this the drug was discontinued and pheniramine, hydrocortisone and combination tablet of levocetirizine and montelukast was administered to treat the rashes. Here pheniramine and levocetirizine act as antihistaminic, hydrocortisone binds to glucocorticoid receptors leading to inhibition of inflammatory factors and montelukast acts as a mast cell stabilizer.

Causality assessment was done using the Naranjo scale and WHO UMC assessment scale.[5,6] The adverse drug reactions was reported by VigiFlow in the pharmacovigilance centre.

Table 1: Naranjo ADR probability scale.

Questions	Yes	No	Do not know	Score
Are there previous conclusive reports on this reaction?	+1	0	0	Yes
Did the adverse event appear after the suspected drug was administered?	+2	-1	0	Yes
Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0	Yes
Did the adverse event reappear when the drug was re-administered?	+2	-1	0	DNK
Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	+2	0	No
Did the reaction reappear when a placebo was given?	-1	+1	0	DNK
Was the drug detected in blood (or other fluids) in concentrations knownto be toxic?	+1	0	0	DNK
Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	DNK
Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	No
Was the adverse event confirmed by any objective evidence?	+1	0	0	No
Total score				6

DNK-Do Not Know

Table 2: WHO UMC causality categories.

Causality term	Assessment criteria
Certain	Event or laboratory test abnormality, with plausible time relationship to drug intake
	Cannot be explained by disease or other drugs,
	Response to withdrawal plausible (pharmacologically, pathologically)
	Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognized pharmacological phenomenon)
	Rechallenge satisfactory, if necessary
Probable/ likely	Event or laboratory test abnormality, with reasonable time relationship to drug intake
	Unlikely to be attributed to disease or other drugs
	Response to withdrawal clinically reasonable
	Rechallenge not required
Possible	Event or laboratory test abnormality, with reasonable time relationship to drug intake
	Could also be explained by disease or other drugs
	Information on drug withdrawal may be lacking or unclear
Unlikely	Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible)
	Disease or other drugs provide plausible explanations
Conditional/ unclassified	Event or laboratory test abnormality
	More data for proper assessment needed, or
	Additional data under examination
Un-assessable/ unclassifiable	Report suggesting an adverse reaction
	Cannot be judged because information is insufficient or contradictory
	Data cannot be supplemented or verified

DISCUSSION

To establish the likelihood of relationship between the drugs and the erythematous maculopapular rash Naranjo scale (Table 1) and WHO UMC scale (Table 2) were used.

The Naranjo algorithm or ADR probability scale is a method used to assess whether there is a causal relationship between an identified untoward clinical event and a drug using a simple questionnaire to assign probability scores.

Interpretation of scores in Naranjo scale

Total score ≥9: *Definite:* The reaction (1) followed a reasonable temporal sequence after a drug or in which a toxic drug level had been established in body fluids or tissues, (2) followed a recognized response to the suspected drug, and (3) was confirmed by improvement on withdrawing the drug and reappeared on re-exposure.

Total score 5-8: Probable: The reaction (1) followed a

reasonable temporal sequence after a drug, (2) followed a recognized response to the suspected drug. (3) was confirmed by withdrawal but not by exposure to the drug, and (4) could not be reasonably explained by the known characteristics of the patient's clinical state.

Total score 1-4: Possible: The reaction (1) followed a temporal sequence after a drug, (2) possibly followed a recognized pattern to the suspected drug, and (3) could be explained by characteristics of the patient's disease.

Total score <0: Doubtful: The reaction was likely related to factors other than a drug.

In this case the causality assessment using Naranjo scale (Score 6) and WHO-UMC scale indicates probable relationship.

Gabapentin and nortriptyline combination is the first line treatment for management of neuropathic pain. The common adverse drug reactions associated with gabapentin are ataxia, dizziness, fatigue, somnolence, fever, nystagmus, peripheral oedema, hostility and hyperkinesia (paediatric), nausea and vomiting, tremor, asthenia, diplopia, diarrhoea, xerostomia, infection, amblyopia and headache.[7]

The most common adverse effects of nortriptyline include downiness, xerostomia, dizziness, constipation, blurred visions, palpitations, tachycardia, impaired coordination, increased appetite, nausea/vomiting, confusion, restlessness, insomnia, anxiety, urinary retention, rash, urticaria, pruritus, weight gain.[2]

CONCLUSION

Literature search did not show such studies for the combination of gabapentin and nortriptyline. Hence monitoring is essential for any ADRs while using combination of gabapentin and nortriptyline and in case of ADRs one must discontinue the drug and report it to the pharmacovigilance centre.

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