Serotonin Syndrome ascribed to Combined Selegeline and Amitriptiline: A Case Report with an Indonesian Parkinson patient

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ABSTRACT:

A-62-year-old man, diagnosed as Parkinson patient, reported to hospital B after having taking medication prescribed by two different doctors. Among his medication, it was found that he consumed both selegeline 5mg 1 tablet and amitriptyline 25mg 0,5 tab at 07.00 AM and 01.00 PM. After three weeks consuming these medications, his movement stability at his left and right leg was deteriorated, felt confusion, tremor on his hand, restless leg and agitation. This case report aims to analyze the drug related problems. Medscape drug interaction checker and Naranjo scale was used to examine the drug related problems. Literature review from guideline and journal was performed to find out the reason of drug related problems. Significant interaction was found and known as the cause of increased brain serotonin level. Probable adverse drug reaction was demonstrated on Naranjo scale. In several cases reports, the condition was reported as serotonin syndrome.

Keywords: Serotonin Syndrome, Parkinson, Selegiline, Amitriptiline

1 INTRODUCTION

The serotonin syndrome is a life-threatening condition caused by increased serotonergic activity. (Boyer and Shannon, 2005) Three main symptom of serotonin syndrome are altered mental status, autonomic hyperactivity, and neuromuscular abnormalities (Table 1). Sign of serotonin syndrome vary in range, from mild cases such as tremor and diarrhea to delirium, neuromuscular rigidity, hypertension, tachycardia, and coma in severe cases (Abadie, Kaye and Kaye, 2013; Boyer and Shannon, 2005)

Table 1. Symptoms of Serotonine Syndrome

Altered mental status	Confusion, Hypomania, Hallucinations, Agitation, Slightly slurred speech, Headache, Delirium, Coma
Automic hyperactivity	Syncope, Shivering, Sweating, High fever, Hypertension, Tacycardia, Nausea, Diarrhea, Mydriasis
Neuromuscular abnormalities	Muscular rigidity, Myoclonus, Tremor

The actual prevalence of serotonin syndrome is unknown. The number of unreported cases is greater than the reported cases. Serotonin Syndrome is often undiagnosed and it is attributed to be a general side effect of certain treatment. (Abadie, Kaye and Kaye, 2013)

It has been reported since 1950s that there is a risk of developing serotonin syndrome if a patient consumed ‘combined treatment’ which both induced excess intra-synaptic serotonin or 5-hydroxytryptamine(5-HT). (Gilman, 1999) Parkinson disease patient is one example of patient who use those treatment combinations. The typical motor disease with some characterize non-motor features such as depression lead the treatment of Parkinson disease patient into a combination of both MAO-inhibitor and antidepressant. It is known that the combination of MAO-inhibitor and antidepressant theoretically

increased the risk of serotonin syndrome when it is used concurrently. (Setter and Cerruto, 2010)
In Indonesia, this combination is widely used in Parkinson disease patients. In contrary, serotonin syndrome has not been reported and the information related to this syndrome is quite rare. This case report aim to analyze the drug related problem and increasing the awareness of serotonin syndrome in Indonesian Parkinson disease patients.

2 CASE PRESENTATION

A-62-year-old man was diagnosed by doctor as Parkinson disease patient since December 2014. He was diagnosed abroad Indonesia, and was given Parkinson medication. After 1 year taken the medication, there was no improvement on his condition. Afterwards, he come to Hospital A in Indonesia to see neurologist. According to the patient wife's information, the Indonesian neurologist told him to continue his medicine from the previous prescription and add some other medication to improve patient's condition. The list of patient's medication schedule was listed on Table 2. Among the medications, it is found that selegiline and amitriptyline was prescribed concurrently both at 07.00 AM and 01.00 PM.

The first 2 weeks after taking the medication, the patient's condition is getting better. But after three weeks, his wife said his condition was worsen. There was a deterioration in his movement stability at both his left and right leg. The patient also complained about feeling confusion, tremor on his hand, restless leg and agitation. His wife come to hospital B, to get second opinion from another neurologist. The neurologist at hospital B asked clinical pharmacy to assess his husband medication.

Table 2. Patient's Medication Schedule

Time	Name of medicine	Amount (tablets)
Morning (07.00 am)	Pramipexole 0.75 mg Carbidopa + Levodopa + Entacapone 100/125/200 Selegiline Amitryptiline 25 mg	1 1 1 0.5
Afternoon (01.00 pm)	Carbidopa + Levodopa + Entacapone 100/125/200 Selegiline Amitryptiline 25 mg	1 1 0.5
Evening (06.00 pm)	Carbidopa + Levodopa + Entacapone 100/125/200 Bromocriptine 2.5 mg	1 1

3 METHODS

To analyze the drug related problems. First, we input all medications taken by the patients to *Medscape* drug interaction checker. Next, literature review from guideline and journal was performed to find out the reason or information related to the interaction. After that, Naranjo scale was used to examine the class of adverse drug reaction related to interaction. Last, the result of this analyses was presented as a case report.

4 RESULTS AND DISCUSSIONS

Medscape drug interaction checker reported that there were four interactions found in the patient's medication. The interactions summarized in Table 3. From the interactions, it was found that patient complains were similar with the effect of interaction number 1.

Table 3. Drug Interaction Checker Results *(Medscape drug interaction checker, 2017)*

No	Drug Combination	Type of Interaction	Information
1	Selegiline and Amitriptyline	Contraindicated	Concurrent use or use within 14 days of Selegiline and Amitriptyline the combination is contraindicated. Both medications can increase serotonin levels.
2	Selegiline and Levodopa	Contraindicated	Selegiline and Levodopa is contraindicated because both has a pharmacodynamics synergism effect. It may increase the possibility of developing acute hypertension episode. Concominant therapy with selegiline and carbidopa-levodopa is associated with severe orthostatic hypotension.

3	Bromocriptine and Levodopa	Monitor Closely	Combination of Bromocriptine and Levodopa both increase dopamine effect. The combination is known to give therapeutic effect in Parkinson patient and may lower levodopa doses. Dosage should be carefully titrated during concomitant treatment and patients should be monitored closely.
4	Levodopa and Pramipexole	Monitor Closely	Combination of levodopa and pramipexole increase dopaminergic effects

Selegiline is used in Parkinson management in which levodopa/carbidopa therapy is deteriorating. Selegiline is categorized as anti-parkinson's agent which inhibited monoamine oxidase activity (MAO inhibitor). Monoamine oxidase was known as an enzyme which is used in degradation of monoamine such as norepinephrine, dopamine and serotonin. (Dana, Fuller, Goldman, Golembiewski, Gonzales, Lowe, Snoke, 2013) In Parkinson disease, it is necessary to used MAO inhibitor to block the degradation of dopamine. Inhibition of MAO activity indirectly increases intra-synaptic serotonin level. MAO inhibitor can be classified according to its selectivity into three groups, they were Non-selective MAO inhibitor, MAO-A inhibitor, and MAO-B inhibitor. Selegiline is included in selective MAO-B inhibitor.

Amitriptyline is indicated as antidepressant agent. It was categorized as tricyclic antidepressant (TCA). The mechanism of action of this drug was inhibiting the re-uptake of monoamines such as norepinephrine, dopamine and serotonin from intra-synaptic area to presynaptic. (Dana, Fuller, Goldman, Golembiewski, Gonzales, Lowe, Snoke, 2013) This medication is prescribed as a treatment to non-motor features symptom such as depression which also presented in Parkinson disease patients. Inhibition of serotonin reuptake from intra-synaptic mean that the level of intra-synaptic serotonin would be increased.

The literature review concluded that combination of both selegiline and amitriptyline both had the same effect on intra-synaptic serotonin level. Richard, Kurlan, Tanner *et al*, 1997 stated that this combination was contraindicated due to potentially serious CNS toxicity known as serotonin syndrome. It has been reported that the combination would result in tremors, agitation, restlessness, muscle rigidity, and incoordination which was also happened in this 62-year-old patient. (Richard, Kurlan, Tanner *et al*, 1997)

Similar case was also reported by Hinds, Hiller and Wiles on 2000. 42-year-old woman presented with symptom of confusion, immobility, and tremor on her upper limbs. She was diagnosed as Parkinson disease patients and has also developed severe depression. Her doctor prescribed selegiline 10 mg once daily as her anti-parkinson's agent and nortriptyline 75 mg daily as her antidepressant agent. Nortiptyline was known to be classified in the same group as amitriptyline, which was TCA. A provisional diagnosis of serotonin syndrome was made and both treatments were stopped. (Hinds, Hillier, Wiles, 2000)

An algorithm to detected serotonin syndrome has been published by Boyer and Shannon, 2005. This tool was reported to be 84% sensitive and 97% specific to detect serotonine syndrome. The result of the analysis was shown on figure 1. Another algorithm called the Hunter Serotonin Syndrome Criteria was also used was published by Buckley, Dawson, and Isbister, 2014. In this research, this algorithm was also used to confirmed serotonin syndrome in this Indonesian Parkinson patient. The algorithm showed more clearly that the patients has a potential sign to be stated as a patient with seroto-nin syndrome or also known as serotonin toxicity. Agitation and tremor which were two symptoms that presented in this patient according to the article published by Buckley, Dawson and Isbister, 2000 could be a sign of moderate serotonin syndrome. In the article, it was said that if a patient developed tremor and agitation, it was indicated that the level of serotonin has been risen 5-10 times the normal levels. The result of the analysis was summarized in figure 2.

Figure 1. The analysis result of patient's condition using sero

tonin syndrome's algorithm of Boyer and Shanon, 2005. It could be concluded that the patient possibly developed serotonin syndrome. The yellow boxes demonstrated the analysis result.

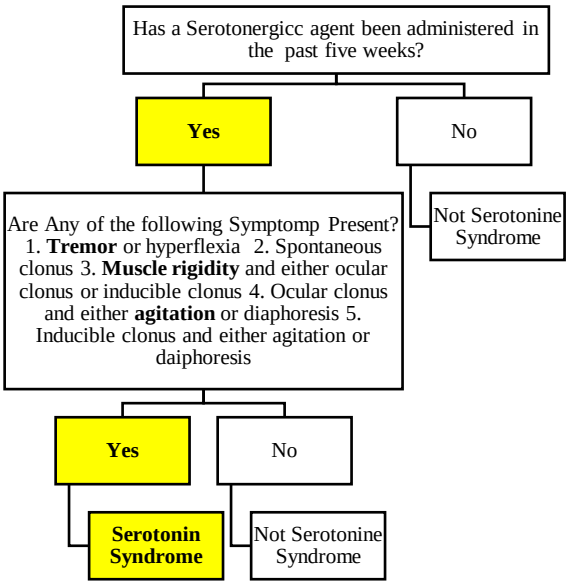

Figure 2. The analysis results of patient's condition using Hunter Serotonin Syndrome Criteria. It could be concluded from the criteria that this patient had a possibility to developed serotonin syndrome. The red boxes demonstrated the analysis results. (Buckley, Dawson and Isbister, 2000)

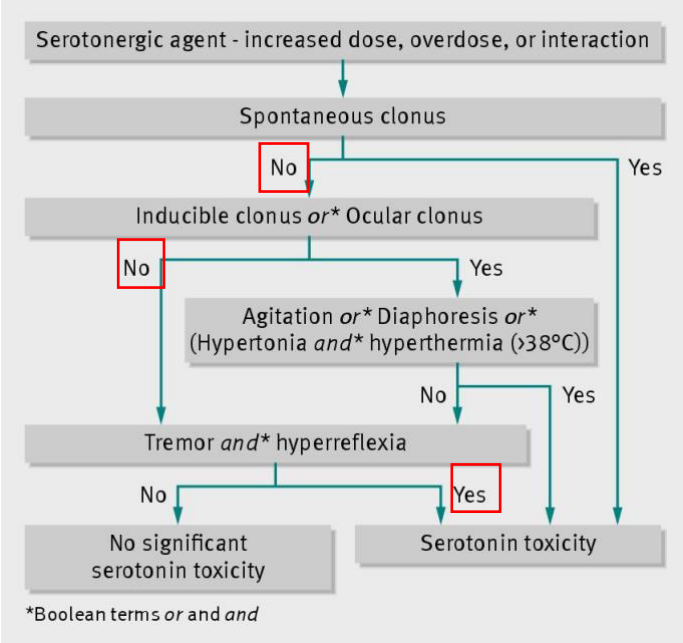

Table 4. Naranjo Scale Result

Naranjo Adverse Drug Reaction Probabillity Scale				
Question	Yes	No	Do Not Know	Score
1. Are there previous conclusive report on this reaction	+1	0	0	+1
2. Did the adverse event appear after the suspected drug administer?	+2	+1	0	+2
3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0	0
4. Did the adverse event reappear when the drug was re-administered	+2	-1	0	0
5. Are there alternative causes (other than the drug) that could on their own have caused the reaction	-1	+2	0	+2
6. Did the reaction reappear when placebo was given	-1	+1	0	0
7. Was the drug detected in blood (or other fluids) in concentrations known to be toxic?	+1	0	0	0
8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased	+1	0	0	0
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	0

10. Was the adverse drug reaction confirmed by any objective evidence?	+1	0	0	+1
Total Score				+6

Naranjo scale is known as a tool to assess the possibility of medication developing adverse drug reaction. In this case report, we checked the possibility of selegiline in combination with amitriptyline developed serotonin syndrome using this tool. The calculation of this case report demonstrated a total score 6. This total score was in the range of 5-8, which meant probable adverse drug reaction caused by combination of both drugs. The result was presented in table 4.

The Medscape drug interaction checker, literature review, algorithm from several scientific articles, and Naranjo scale had shown supporting results which indicated this 62-year-old man was developing serotonine syndrome. According to Buckley, Dawson, and Ibster, 2014 Serotonin syndrome in moderate cases as predicted in this patient, usually resolves in one or three days after stopping the serotonergic drugs. It was suggested to both the neurologist of hospital B to stop selegiline and amitriptyline.

The case report was the pioneer case report of serotonin syndrome in Indonesian patient with Parkinson disease. This research could be a good example to increase the awareness of pharmacist, doctor and other health care provider of the possibility of serotonin syndrome if selegiline and amitriptyline was combined.

The limitations of this case report were this case report only consist of one case and was written before the monitoring after the intervention was performed. It is also suggested to record more cases to record the prevalence of serotonin syndrome especially in Indo

nesian patients. Medication screening of Parkinson treatment combination should be performed continuously by all health care provider, especially pharmacist.

5 CONCLUSION

Drug related problems (DRP) was found in this case report. According to the patients complain, the drug related problem was induced by the interaction of selegiline and amitriptyline. This interaction was a probable cause of an adverse drug reaction called serotonin syndrome. This condition has been reported in several cases in the form of objective evidence. Increasing pharmacist and other health care provider awareness about serotonin syndrome in Indonesian Parkinson disease patients would be important to optimized patient's clinical outcome.

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