SciMedCentral

Journal of Pharmacology & Clinical Toxicology

Case Series

Treating 'Devil's Breath' Intoxication: Use of Rivastigmine in Six Patients with Toxic Psychoses Due to Non Pharmaceutical Scopolamine

Ignacio Sandia S[1]*, Jorge Ramírez V[1], Javier Piñero A[1], and Trino Baptista T[2]

[1]*Department of Medicine, University of The Andes, Venezuela*
[2]*Department of Physiology, University of The Andes, Venezuela*

***Corresponding author**
Ignacio Sandia S, UDA-Psiquiatría, Mezzanina, Hospital Universitario de Los Andes. Av. 16 de Septiembre. Mérida, 5101,Venezuela, Tel: 582403228//+584143742665; Email: i.sandia@ula.ve

Submitted: 20 July 2018

Accepted: 30 July 2018

Published: 31 July 2018

ISSN: 2333-7079

Keywords
- Scopolamine hydrobromide
- Rivastigmine
- Antidotes
- Antipsychotics agents
- Brief psychiatric rating scale
- Emergency service hospital

Abstract

We here report a series of six patients who were admitted at a hospital's emergency room because of voluntary or involuntary intoxication with non-pharmaceutical scopolamine preparations known as '"Devil's Breath". Physostigmine, the antidote of choice in such cases, was not available at that institution. In four of these cases, psychotic symptoms did not improve after four days of treatment with appropriate doses of atypical antipsychotics (risperidone, olanzapine or quetiapine). The antipsychotic medication was then suspended in each case, and a transdermal patch of 10 cm2 of rivastigmine (equivalent to 9.5 mg of the drug) was indicated as monotherapy. The remaining two subjects did not receive any antipsychotic treatment but were administered rivastigmine immediately upon their arrival at the emergency room. Mental status was assessed with the Brief Psychiatric Rating Scale (BPRS) at baseline and on the third and fifth day. The BPRS scores significantly decreased when assessed on days 3 and 5 ($p = 0.012$). We argue that rivastigmine was pivotal in the fast and efficient resolution of these cases of intoxication with non-pharmaceutical scopolamine preparations.

INTRODUCTION

Scopolamine is a muscarinic antagonist widely known outside the scientific community as 'Devil's breath' or 'Burundanga' (among other names) that denote its alkaloid cognitive inhibition properties when used for criminal purposes [1,2]. The botanical genres Datura and Brugmansia are the main natural suppliers of these highly toxic alkaloids [3], and poisoning with these plants is not uncommon [4].

Because of its anticholinergic power and parasympathetic activity, scopolamine has been found to be useful in clinical practice [5], and to be especially effective to prevent motion sickness [6]. It is moreover well known that the cholinergic hypofunction induced by scopolamine produces a loss of the emotional excitation stimulating effect in memory [7]. This seems to be the main effect sought out by criminals who have used preparations of the substance to commit various crimes in both Europe and the Americas [8,9] .

Scopolamine intoxication is characterized by being dose-dependent with specific central and peripheral symptoms. Scopolamine causes a central and peripheral blockade of the muscarinic receptor causing restlessness, excitement, hallucinations, euphoria, and disorientation. Moreover, disturbances in level of consciousness at varying degrees and respiratory depression are not uncommon [10].

At proper doses physostigmine is, inter alia, the antidote of choice for scopolamine intoxication [11,12], but, because of the drug unavailability at the time of the study, the patients reported here --who had been intoxicated with non- pharmaceutical preparations of scopolamine--could not be treated with physostigmine.

Rivastigmine administration was decided because of its composition and properties similar to those of physostigmine [12,13]. Indeed, its combination with atypical antipsychotics has been well documented in the management of psychotic agitation in cases of dementia [14,15], but not in intoxication cases such as those reported here. Cases of scopolamine intoxications have been treated with other cholinesterase inhibitors, such as galantamine [16], and donezepil [17].

PATIENTS AND EXPERIMENTAL PROCEDURES

Six patients (all singles, 03 males, 03 females; aged: 17 ± 1,8 years) were admitted at the Emergency Unit of the

University Hospital of The Andes (Mérida, Venezuela) because of an intoxication with non-pharmaceutical preparations of scopolamine. The emergency treatment -- which included general detoxification measures, an initial biomedical and psychosocial evaluation, and forced diuresis with matched hydration-- did not solve the psychiatric symptoms in spite of the fact that it improved the patients' overall conditions, including the mixed alteration of their state of consciousness (lucidity, orientation and memory). Four of the patients were medicated with atypical antipsychotics for at least four days, but no therapeutic response was observed. The remaining two patients did not receive any antipsychotics. None of the patients presented Delirium due to scopolamine (mixed disturbance of consciousness) as it is described in the literature [5,18], and the psychotic symptoms were the main concern at the Emergency Unit. All the subjects were thus referred to the Psychiatric Emergency Unit of that same Institution. A before/after pre - experimental study was designed.

So as to discard kidney, liver or any other pathologies that could explain our patients' symptomatology, the following laboratory tests were performed on the six subjects: red blood cell count, hemoglobin, hematocrit, white blood cell count and distribution, transaminase, creatinine, urea, baseline glycaemia, urinalysis and blood screening for marijuana, cocaine, opiates and benzodiazepines metabolites. No patient presented respiratory depression, stupor or coma, and all of them were treated according to the treatment guidelines of the University Hospital of the Andes Psychiatry Unit.

Laboratory values of the substance were not determined. However, it is well known that urine concentrations of scopolamine may range from 32.4 to 186.4 ng /mL in cases of intoxication due to the ingestion of plants containing the substance [4]. Moreover, a series of scopolamine-facilitated robberies reported a concentration of scopolamine in blood of 0.30mg/L, about 3000 times higher than the average therapeutic level of 0.0001mg/L [19].

Once the protocol was accepted, the antipsychotic medication was suspended (when applicable), and the six patients were treated once daily and for five days with 10cm^2 transdermal patches equivalent to 9.5 mg of rivastigmine.

Following the Ethics Committee of the University Hospital of The Andes recommendations and the Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects (WMA 2015), all the patients and/or their legal representatives were informed about the aspects related to this research, including the protocol, risks, goals, confidentiality, and access to the research results,

The level of psychopathology was assessed with the Brief Psychiatric Rating Scale (BPRS) of 18 items quantified with a Likert scale of 1-7 [20]. In the present study, a validated version for the Spanish language was used [21]. The total score has a maximum of 126 points; the subscales of positive and negative symptoms (each one with 4 items) have a maximum score of 28 points. The BPRS scale was applied on the first, third and fifth day of treatment.

The SPSS statistical package, version 22, was used to organize the data obtained. The BPRS score at baseline and throughout the treatment was analyzed using Friedman's non-parametric tests as well as the Wilcoxon Sign rank test for comparison of specific treatment intervals. Statistical significance was set at $p < 0.05$.

RESULTS

In these subjects, the scopolamine route of entry to the organism was either involuntary (the patient had been a victim of premeditated poisoning) or voluntary since it is well known that the substance can also be used for fun or in canonical ceremonies. In all six cases, the scopolamine preparations had no authorized pharmaceutical origin and their form of preparation was unknown, although the literature reports cases of extraction from over the counter preparations [22], or as botanical extractions [23].

The six subjects were adolescents and single. Five (83 %) were unemployed. The sex distribution was uniform, and in 50% of the cases the use of scopolamine was involuntary. Of the six subjects, two did not receive any antipsychotic medication, two were administered risperidone (2-6mg / day), one was given olanzapine (10-20mg/day), and another one received a combination of quetiapine (200-300 mg/day) plus risperidone (2-6 mg/day).

Before starting the treatment with rivastigmine (baseline conditions), the score on positive symptoms was much higher than that on negative symptoms: 23.8 ± 1.6 vs. 15.3 ± 2.5, Mann-Whitney U test, $z = 2.9$, $p = 0.004$. This may be a pointer of the clinical picture of this type of intoxication. Treatment with rivastigmine was associated with a significant decrease in the overall score ($p=0.002$) and in the subscales for positive and negative symptoms ($p = 0.003$ for both type of symptoms) (Figure 1).

On the following items of the scale, no significant decrease was detected in the individual scores: basal vs. day 3: items 1 (somatic concern), 5 (self-deprecation and feelings of guilt), 6 (somatic tension / anxiety), 7 (mannerisms and strange postures) and 9 (depressive mood); basal vs. day 5: items 5 and 16 (dulling / affective flattening).

DISCUSSION

The present study demonstrates the clinical effectiveness of transdermal patches of rivastigmine in the treatment of non-pharmacological scopolamine intoxication. This is an encouraging finding that will help improve the treatment of a medically unrecognized intoxication with psychiatric symptoms that is often reported in the media [23-25].

The beneficial effect of transdermal rivastigmine patches was evident both on the global BPRS scale and on the subscales for positive and negative symptoms. It is important to emphasize that the beneficial effect was greater on the positive than on the negative symptoms, which allows a better clinical characterization of the psychopathological effects of non-pharmacological scopolamine.

The improvement of the psychotic symptoms in the six cases reported here could be explained by the fact that the majority of our patients had received antipsychotics prior to

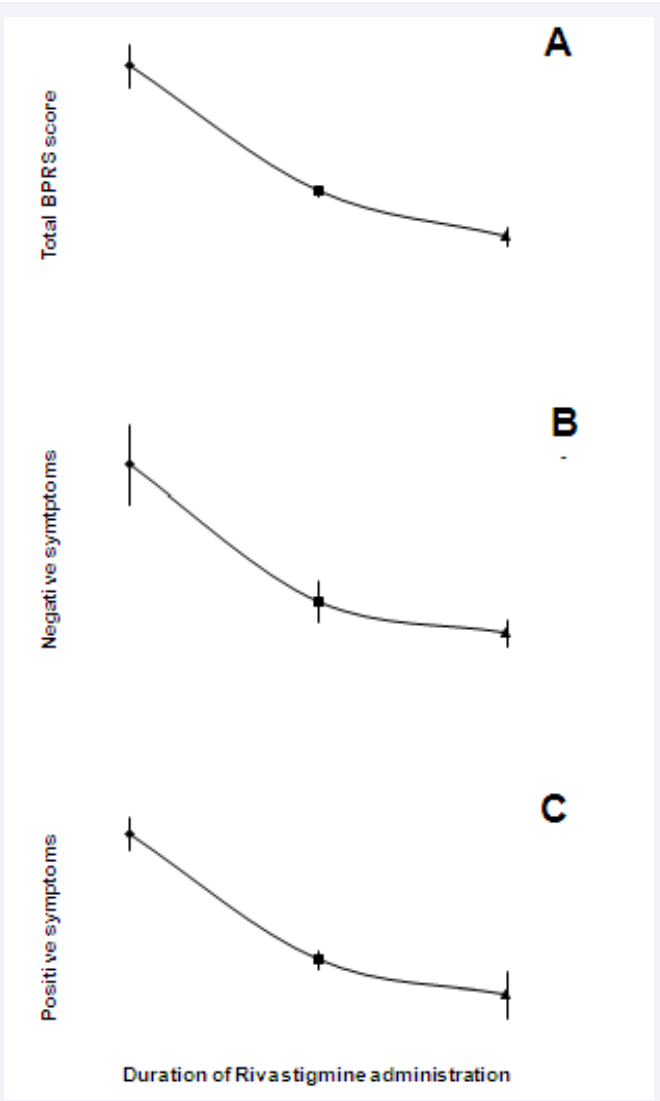

Figure 1

(A) Friedman test: χ^2 (2) = 12.0, p = 0.002; Wilcoxon test: basal vs. day 3: Z = 2.2, p = 0.028; basal vs. day 5 and day 3 vs. day 5: Z = 2.1, p = 0.019.

(B) Friedman test: χ^2 (2) = 11.6, p = 0.003: Wilcoxon test: basal vs. day 3: Z = 2.2, p = 0.027; basal vs. day 5: Z = 2.1, p = 0.026; day 3 vs. day 5 = 2.0, p = 0.039.

(C) Friedman test: χ^2 (2) = 11.5, p = 0.003: Wilcoxon test: basal vs. day 3: Z = 2.2, p = 0.026; basal vs. day 5: Z = 2.2, p = 0.028; day 3 vs. day 5 = 2.0, p = 0.04.

the administration of rivastigmine. However, previous research has shown that the mechanism by which psychotic symptoms occur in scopolamine intoxication is due to the drug anti-muscarinic effects, and that when those symptoms are treated with antipsychotics, the response is not the expected one unless a cholinesterase inhibitor is added [26,27].

Although the ratio response of scopolamine-rivastigmine has already been tested in experimental animals [28], the present study is the first to suggest that rivastigmine without antipsychotics could be effective in this type of intoxications in humans.

We argue that the improvement in psychotic symptoms (as revealed by the BPRS overall and sub-scale results) can only be explained by the beneficial effect of the transdermal patches of rivastigmine since it is the only pharmacological variable introduced in the treatment, especially in the four subjects who did not respond to antipsychotics for over 72 hours.

It is well known that the addition of cholinesterase inhibitors to antipsychotics improves symptoms [14], but not under the circumstances reported here where the muscarinic antagonistic properties of the antipsychotic would have accentuated the anti-cholinergic symptoms produced by scopolamine poisoning. It is worthwhile emphasizing that the response to the transdermal patches of rivastigmine was identical in the two cases where no atypical antipsychotic was prescribed.

It could be argued that, since our six subjects were young and healthy, their improvement was due to the substance elimination. However, because the metabolism of scopolamine can take up to 108 hours [5,29], our patients' improvement can only be explained by the therapeutic effect of rivastigmine.

It should finally be emphasized that our patients' improvement was similar for the subjects who were given the transdermal patch several days after their arrival at the Hospital Emergency Unit as for those who were immediately given the patch upon admission. As we stated before, previous research on animal models has shown that rivastigmine reverts the cognitive effects of scopolamine [30-32], but we would like to suggest here that rivastigmine could also reverse psychiatric symptoms induced by scopolamine intoxication.

Given the efficacy of rivastigmine transdermal patches and its ease of administration, further research should be conducted on larger samples of patients. Additional research should also aim to compare the efficacy of rivastigmine vs that of physostigmine and to determine rivastigmine response time course.

AUTHOR DISCLOSURE

Role of funding source

There was no Funding for this study other than the University Hospital of the Andes (IAHULA) resources; the IAHULA had no further role in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

Contributors

Ignacio Sandia, Jorge Ramirez and Javier Piñero designed the study and wrote the protocol. Jorge Ramirez and Javier Piñero collected the data. Jorge Ramirez and Ignacio Sandia managed the literature searches and analyses. Trino Baptista the statistical analysis, Ignacio Sandia wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

ACKNOWLEDGMENTS

We are most grateful to our patients and their relatives for their cooperation, and to Françoise Meyer our trained scientific editor.

- 9. HighlightsScopolamine preparations known as Devil's

Breath are reportedly used by criminals.

- An approach to the psychopathological effects of non-pharmacological scopolamine.
- A treatment for a medically unrecognized intoxication often reported in the media.
- Rivastigmine alone might reverse psychiatric symptoms induced by scopolamine.

REFERENCES

1. Stebner B. The most dangerous drug in the world: 'Devil's Breath' chemical from Colombia can block free will, wipe memory and even kill. The Daily Mail. 2012.
2. Damin C. Qué es y cómo actúa la Escopolamina, "Burundanga". 2015.
3. Alvarez L. Borrachero, cacao sabanero o floripondio (brugmansiaspp.). Un grupo de plantas por redescubrir en la biodiversidad latinoamericana. Cultura y Droga. 2008; 13: 77-93.
4. Papoutsis I, Nikolaou P, Athanaselis S, Stefanidou M, Pistos C, Spiliopoulou C, Maravelias, et al. Mass intoxication with Datura innoxia--case series and confirmation by analytical toxicology. C. ClinToxicol (Phila). 2010; 48: 143-145.
5. Renner UD, Oertel R, Kirch W. Pharmacokinetics and pharmacodynamics in clinical use of scopolamine. Ther Drug Monit. 2005; 27: 655-665.
6. Brainard A, Gresham C. Prevention and Treatment of Motion Sickness. Am Fam Physician. 2014; 90: 41-46.
7. Kamboj SK, Curran HV. Neutral and emotional episodic memory: global impairment after lorazepam or scopolamine. Psychopharmacol (Berl). 2006; 188: 482-488.
8. Peatfield, Villalón. Headache after exposure to 'date-rape' drugs. Springer Plus. 2013; 2: 39.
9. Draper L. Does the "Devil's Breath" Drug Really Exist? Newsweek. Europe Edition. 2015.
10. Apfel C, Zhang K, George E, Shi S, Jalota L, Hornuss C, et al. Transdermal scopolamine for the prevention of postoperative nausea and vomiting: a systematic review and meta-analysis. ClinTher. 2010; 32: 2502.
11. Gómez CU. Escopolamina, in: Ministerio de la protección Social (Eds.) Guías para el manejo de urgencias toxicológicas. Chapter 3.7 Bogotá, Colombia: Imprenta Nacional de Colombia; 2008.
12. Barak D, Ordentlich A, Stein D, Yu Q, Greig N, Shafferman A. Accommodation of physostigmine and its analogs by acetylcholinesterase is dominated by hydrophobic interactions. Biochem J. 2009; 417: 213-222.
13. Buccafusco J. The Revival of Scopolamine Reversal for the Assessment of Cognition-Enhancing Drugs, in: Buccafusco JJ (Ed) Methods of Behavior Analysis in Neuroscience Chapter 17. Boca Raton (FL): CRC Press/Taylor & Francis. 2009.
14. Holmes C, Wilkinson D, Dean C, Clare C, El-Okl M, Hensford C, et al. Risperidone and rivastigmine and agitated behaviour in severe Alzheimer's disease: a randomised double blind placebo controlled study. Int J Geriatr Psychiatry. 2007; 22: 380-381.
15. Rocca P, Marino F, Montemagni C, Perrone D, Bogetto F. Risperidone, olanzapine and quetiapine in the treatment of behavioral and psychological symptoms in patients with Alzheimer's disease: preliminary findings from a naturalistic, retrospective study. Psychiatry Clin Neurosci. 2007; 61: 622-629.
16. Cozanitis DA. Galanthaminehydrobromide, a longer acting anticholinesterase drug, in the treatment of the central effects of scopolamine (Hyoscine). Anaesthesist. 1977; 26: 649-650.
17. Snyder PJ, Bednar M, Cromer JR, Maruff P. Reversal of scopolamine-induced deficits with a single dose of donepezil, an acetylcholinesterase inhibitor. Alzheimer's Dement. 2005; 1: 126-135.
18. Corallo CE, Whitfield A, Wu A. Anticholinergic syndrome following an unintentional overdose of scopolamine.Ther Clin Risk Manag. 2009; 5: 719-723.
19. Lusthof K, Bosman I, Kubat B, Vincenten-van Maanen M. Toxicological results in a fatal and two non-fatal cases of scopolamine-facilitated robberies. Forensic Sci Int. 2017; 274: 79-82.
20. Overall, John E, Gorham, Donald R. The Brief Psychiatric Rating Scale. Psychological Reports. 1962; 10: 799-812.
21. Sánchez R, Ibáñez MA, Pinzón A. Análisis factorial y validación de la versión en español de la escala Brief Psychiatric Rating Scale en Colombia. Biomédica. 2005; 25: 120-128.
22. Kummer S, Rickert A, Daldrup T, Mayatepek E. Abuse of the over-the-counter antispasmodic butylscopolamine for the home synthesis of psychoactive scopolamine.Eur J Pediatr. 2015; 175: 1019-1021.
23. Bernal A, Gómez López S, Acosta M. Neuropsychological, neurological and psychiatric implications in a case of poisoning scopolamine. Universidad de San Buenaventura, Bogotá – Colombia. Psychol Av Discip. 2013.
24. Lares V. Venezuela: alerta por burundanga. Diario El Tiempo. 2006.
25. Samuel, Henry. Three arrested in Paris over 'devil's breath' drug that turns victims into willing 'zombies' The Telegraph News. 2015.
26. Yeomans JS. Role of tegmental cholinergic neurons in dopaminergic activation, antimuscarinic psychosis and schizophrenia. Neuropsychopharmacology. 1995; 12: 3-16.
27. Barak S, Weiner I. Scopolamine Induces Disruption of Latent Inhibition which is prevented by Antipsychotic Drugs and an Acetylcholinesterase Inhibitor. Neuropsychopharmacology. 2007; 32: 989-999.
28. Bejar C, Wang R, Weinstock M. Effect of rivastigmine on scopolamine-induced memory impairment in rats.Eur J Pharmacol. 1999; 383: 231-240.
29. TOXNET Hazardous Substances Data Bank [Internet]. Bethesda (MD): National Library of Medicine (US); (Last Revision Date 2009); Scopolamine CASRN: 51-34-3; Hazardous Substances Databank Number: 4074.
30. Deiana S, Harrington CR, Wischik CM, Riedel G. Methylthioninium chloride reverses cognitive deficits induced by scopolamine: comparison with rivastigmine. Psychopharmacology (Berl). 2009; 202: 53-65.
31. Müller J, Wanke K. Toxic psychoses from atropine and scopolamine. Fortschr Neurol Psychiatr. 1998; 66 : 289-295.
32. Le Garff E, Delannoy Y, Mesli V, Hédouin V, Tournel G. Forensic features of a fatal Datura poisoning case during a robbery. Forensic Sci Int. 2016; 261: e17-21.

Cite this article

Ignacio SS, Jorge RV, Javier PA, Trino BT (2018) Treating 'Devil's Breath' Intoxication: Use of Rivastigmine in Six Patients with Toxic Psychoses Due to Non Pharmaceutical Scopolamine. J Pharmacol Clin Toxicol 6(4):1115.