

Juan Pablo Carrasco^{1,2,*}
Eduardo Jesús Aguilar^{1,2,3,4}

Antibiomania: A Case Report of a Manic Episode Potentially Induced by the Interaction of Clarithromycin and Amoxicillin during *H. Pylori* Eradication Therapy

¹Department of Psychiatry, Hospital Clínico Universitario de Valencia, 46010 Valencia, Spain

²Biomedical Research Institute INCLIVA, 46010 Valencia, Spain

³Department of Psychiatry, Faculty of Medicine of Valencia, 46010 Valencia, Spain

⁴Biomedical Research Networking Centre in Mental Health (CIBERSAM), 28029 Madrid, Spain

Abstract

Antibiomanic episodes, or as the DSM-5 refers to them, drug-induced manic episodes, pose a clinical challenge that is still poorly understood. There is insufficient information on the most common clinical presentation, patient profile, or underlying aetiopathogenic mechanisms. We present the clinical case of a 67-year-old woman who, after starting treatment (clarithromycin and amoxicillin) for the eradication of *Helicobacter pylori*, bacteria presented with a brief manic episode, which resolved after withdrawal of both drugs and with antipsychotic treatment. The possible interaction of both drugs, as GABA antagonists, in the generation of such episodes is discussed, and the clinical importance of such episodes in psychiatric emergency departments and liaison and interconsultation psychiatry, is highlighted.

Keywords

antibiomania; treatment-induced manic episode; clarithromycin; amoxicillin; consultation-liaison psychiatry

Corresponding author details: Juan Pablo Carrasco, Department of Psychiatry, Hospital Clínico Universitario de Valencia, 46010 Valencia, Spain; Biomedical Research Institute INCLIVA, 46010 Valencia, Spain. Email: juanpablocarrascopicazo@gmail.com

Introduction

Antibiomania episodes, or as the DSM-5 refers to them, treatment-induced manic episodes, represent a clinical challenge that is still poorly understood. Despite the fact that there are data on the number of cases collected by the State Drug Agencies of different countries [1], there is not enough information on the most common clinical presentation, patient profile, or the aetiopathogenic mechanisms related to them. In addition, practically none of the published cases refer to possible interactions between drugs. In this sense, one case describing a patient who presented with manic episodes, initially while taking clarithromycin, and later while taking amoxicillin-clavulanate, stands out [2]. In recent years, there has been a significant increase in such cases due to the appearance of new antibiotic drugs and the increase in the prescription of these types of treatments [3].

Case Report

The present case describes a 67-year-old patient who was taken by her family, due to behavioural disturbance, to the emergency service of the Hospital Clínico Universitario de Valencia, three days after starting the eradication treatment of *Helicobacter pylori* (*H. pylori*) gastritis (omeprazole 20 mg, clarithromycin 500 mg and amoxicillin 1 g every 12 hours). After an initial clinical evaluation by the emergency general doctors, the patient was admitted to the Internal Medicine service. The first psychiatric evaluation conducted by the consultation-liaison team revealed an increase in psychomotor activity, irritability, logorrhoea, hyperthymic mood, and difficulty falling asleep, as well as auditory hallucinations, mood-congruent mystical delusions,

and delusions of harm. The Young Mania Rating Scale (YMRS) score at the time of evaluation was 32, indicating a manic episode. The examination was completed with a blood analysis that included biochemistry, blood count and coagulation, and PCR for COVID-19, as well as brain MRI, lumbar puncture, and electroencephalogram. None of the results indicated abnormal alterations.

Given the normal results of the complementary tests, the age of the patient, the absence of a history of major affective disorders, and considering the close temporal relationship between the intake of clarithromycin and amoxicillin and the symptomatology, in addition to the rapid improvement after cessation of the treatment, the case was acknowledged as an antibiotic-induced manic episode, a diagnosis of exclusion. We interpreted this event as a probable adverse reaction to the interaction of these drugs, according to the WHO-UMC system for the standardized evaluation of the causality of cases. After the elaboration of this hypothesis, the antibiotic treatment was immediately suspended and Olanzapine (5 mg PO) was prescribed to treat the psychomotor agitation. Twenty-four hours after the withdrawal of clarithromycin and amoxicillin, a rapid improvement was observed, with the cessation of all symptoms, in addition to presenting complete awareness of the full episode.

Discussion

Taking into account the ever-increasing number of reported cases of antibiomania, the cause of the aforementioned episode involves one of the antibiotics that is responsible for most antibiomania episodes (clarithromycin) [4]. However, recent studies highlight the risk of antibiotic interactions in such cases, including cases where one of the antibiotics is amoxicillin [2]. The most interesting aspect of the case lies in the possible pharmacodynamic interaction between the two drugs, which is a frequently underestimated possibility. Different theories have been advanced to explain this association [4]. So far, the one with the highest degree of consensus is the theory that it interacts with GABA receptors [5]. Clarithromycin antagonizes postsynaptic GABA-A receptors in neurons and may cause increased neuronal excitability. In addition, beta-lactams such as amoxicillin could also behave as concentration-dependent GABA antagonists, although they tend to present fewer interactions.

Conclusion

Drug-induced manic episodes are a reality that, given the diagnostic and therapeutic difficulties they pose, must be taken into account in clinical practice, especially in psychiatric emergency and liaison-consultation services. These reactions are typically observed in patients around the age of 50, under treatment regimens that include different antibiotics such as macrolides or quinolones. These antibiotics are used, among others, in the treatment of *H. pylori*. Therefore, knowledge of these treatment regimens is potentially useful in order to perform an early diagnosis. However, more studies are necessary to identify potential mechanisms, the clinical and sociodemographic profile, and the optimal resolution of the treatment-induced manic episodes.

Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Author Contributions

Regarding authors' contribution, JPC made a substantial contribution to the acquisition and analysis of data for the work, drafted the first version and approved the final version of the work; EJA made a significant contribution to the conception and design of the work, reviewing it critically for important intellectual content and approved the final version of the work. Both authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ethics Approval and Consent to Participate

The regulations of the ethics commission of the University of Valencia establish that those studies that do not experiment with humans, animals, or biological samples, or use pathogenic biological agents or genetically modified organisms (article 1, point 3), are exempt from the need for their evaluation for publication. The authors confirm that research protocols regarding informed consent, confidentiality of clinical data and the Helsinki Declaration have been respected.

Acknowledgment

Not applicable.

Funding

This research received no external funding.

Conflict of Interest

The authors declare no conflict of interest.

References

- [1] Abouesh A, Stone C, Hobbs WR. Antimicrobial-induced mania (antibiomania): a review of spontaneous reports. *Journal of Clinical Psychopharmacology*. 2002; 22: 71–81.
- [2] Meszaros EP, Stancu C, Costanza A, Besson M, Sarasin F, Bondolfi G, *et al.* Antibiomania: a case report of clarithromycin and amoxicillin-clavulanic acid induced manic episodes separately. *BMC Psychiatry*. 2021; 21: 399.
- [3] Palleti SK, Wadhwa A, Rasheed AH. The First Case of Ceftazidime-Induced Antibiomania: A Case Report and Literature Review. *Cureus*. 2022; 14: e32904.
- [4] Lambrichts S, Van Oudenhove L, Sienaert P. Antibiotics and mania: A systematic review. *Journal of Affective Disorders*. 2017; 219: 149–156.
- [5] Bichler EK, Elder CC, García PS. Clarithromycin increases neuronal excitability in CA3 pyramidal neurons through a reduction in GABAergic signaling. *Journal of Neurophysiology*. 2017; 117: 93–103.