Rev Med Chile 2023; 151: 1640-1645

Gastroparesis associated to isoniazid. First description

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Conflicto de Interés: ninguno.

Fuentes de apoyo financiero: Este estudio no contó con apoyo financiero de ninguna institución.

Recibido el 07 de noviembre de 2023, aceptado el 18 de enero de 2024.

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Isoniazid, a central compound in the treatment of active or latent tuberculosis, is associated with various adverse reactions, including hepatitis and polyneuropathy. The latter is due to functional pyridoxine depletion and can be avoided by appropriate doses and supplementation with pyridoxine. We present the case of a patient with several previous treatment abandonments for active pulmonary tuberculosis who evolved with late postprandial vomiting due to gastroparesis documented by nuclear medicine gastric emptying tests after a new treatment onset. Gastroparesis improved with discontinuation of isoniazid and levosulpiride, reappeared with re-exposure, and improved with definitive withdrawal of isoniazid. Morbidity associated with vomiting led to prolonged hospitalization and treatment failure without the emergence of antituberculosis drug resistance. The association of gastroparesis with isoniazid was considered definitive when applying at least two causality protocols. Gastroparesis associated with isoniazid should be added to the list of adverse effects associated with this drug, even in patients receiving pyridoxine supplementation. Its recognition is initially clinical, can be confirmed with nuclear medicine studies, and affects the eradication of Mycobacterium tuberculosis.

(Rev Med Chile 2023; 151: 1640-1645)

Key words: *Drug-Related Side Effects and Adverse Reactions; Isoniazid; Gastroparesis; Nuclear Medicine; Tuberculosis.*

Gastroparesia secundaria a isoniazida. Primera descripción

La isoniazida, un compuesto central en el tratamiento de la tuberculosis activa o latente, se asocia a diversas reacciones adversas incluyendo hepatitis y polineuropatía. Esta última obedece a una depleción funcional de piridoxina y puede ser evitada por dosis apropiadas y suplemento con piridoxina. Presentamos el caso de un paciente con varios abandonos previos de tratamiento de tuberculosis pulmonar activa que luego de un nuevo comienzo, evoluciona con vómitos postprandiales tardíos secundarios a una gastroparesia, documentada por exámenes de vaciamento gástrico por medicina nuclear. La gastroparesia mejoró con la suspensión de isonazida y levosulpiride, reapareció con la reexposición ynuevamente mejoró con el retiro definitivo de isoniazida. La morbilidad prolongada asociada a los vómitos generó un fracaso del tratamiento y una hospitalización prolongada, sin emergencia de resistencia a las drogas antituberculosas. La asociación de la gastroparesia con isoniazida fue asignada como definitiva al aplicar al menos 2 protocolos de causalidad. La gastroparesia asociada a isoniazida debe ser agregada a la lista de efectos adversos asociados a este compuesto, incluso en pacientes que reciben suplemento de piridoxina. Su reconocimiento es inicialmente clínico,

puede ser confirmado con estudios de medicina nuclear y también afecta la erradicación de Mycobacterium tuberculosis.

Palabras clave: *Efectos Colaterales y Reacciones Adversas Relacionados con Medicamentos; Gastroparesia; Isoniazida; tuberculosis; Medicina Nuclear;*

Isoniazid (INH), an integral part of first-line drugs for the treatment of active and latent tuberculosis, is associated with a variety of adverse effects, including acute hepatocellular hepatitis due to direct toxicity and polyneuropathy due to pyridoxine deficiency[1-4]. Polyneuropathy is linked to the deficiency of the active compound of vitamin B6: pyridoxal 5' phosphate and its frequency is limited if doses are used according to body weight with vitamin supplementation. Vitamin B6 deficiency occurs due to its increased urinary excretion in conjunction with INH and the irreversible tissular inactivation of pyridoxal 5' phosphate, which acts as an enzymatic cofactor in numerous metabolic processes, including the synthesis of neurotransmitters such as gamma-aminobutyric acid (GABA)[3,4]. Of the vast repertoire of adverse effects of INH, its association with gastroparesis has not been previously reported, and the purpose of this publication is to present a well-documented case of this complication, which impeded the microbiological control of tuberculosis. The Scientific Ethical Committee of the Regional Healthcare Service approved this work.

Case report

At the end of the year 2021, a 37-year-old male patient, a migrant from Ecuador and a resident in Chile for five years, was admitted to our regional hospital. He was unemployed, homeless, and with a history of multiple substance abuse, including tobacco, alcohol, and cocaine pasta base. He had previously been imprisoned. The patient had a history of pulmonary tuberculosis diagnosed in 2018 in Chile, with three therapy abandonments (years 2018, 2020, and 2021), completing 50, 18, and 19 doses of the initial phase each time. Before starting his third treatment in 2021, he presented an Xpert MTB/Rif test without rifampin resistance.

He signaled a 4-6 months history of non-hemoptoic mucopurulent productive cough, dyspnea, fever, and weight loss of approximately 20 kg. The physical examination revealed an emaciated patient weighing 44 kg, hypotensive, and with tachypnea (41/min). Chest computed tomography revealed multiple foci of condensation with diffusely distributed centro-acinar nodules and numerous cavitations. Laboratory tests revealed elevated inflammatory parameters (C Reactive Protein 23.12 mg/dL, erythrocyte sedimentation rate of 114 mm/hour, and leukocytosis of 17,580 cells/μL) with hypoxemia ($Pa0_2$ of 76 mmHg; $PaFiO_2$ 152). He did not have hepatitis B or C virus or HIV co-infection. GenXpert MTB/RIF sputum testing again confirmed the presence of rifampin-susceptible *Mycobacterium tuberculosis* infection.

Tuberculosis treatment was initiated with INH 200 mg/d and rifampin (RMP; 450 mg/d), both orally, associated with parenteral therapy with levofloxacin (500 mg/d) and meropenem 3 g/d. This therapy was maintained until a weight of 45 kg was achieved, changing to a standard 4-drug regimen adjusted by weight with a daily dose of INH of 6.6 mg/kg/d. From the beginning, the patient received oral supplementation with pyridoxine 50 mg/d. The patient evolved with vomiting since the third week, initially assigned to a treatment refusal, which partially responded to ondansetron and which progressed to hyperemesis during week 11, remaining febrile along this period. For this reason, meropenem and linezolid were added i.v. to therapy. The study with digestive endoscopy, ultrasound, and abdominal computed tomography ruled out an endoluminal or visceral pathology as the cause of vomiting. Due to persisting hyperemesis, it was decided to suspend oral therapy at week 14 and to add again i.v. levofloxacin to parenteral therapy. After re-interrogating the patient, a gastric retention syndrome became evident with late postprandial large-volume vomiting, so it was decided to suspend INH and to study liquid (LGE) and solid gastric emptying (SGL) using nuclear medicine scintigraphies. Gastroparesis with impairment

for liquid and solid emptying was confirmed (Table 1)[5], and levosulpiride was added to therapy with a progressive clinical improvement, which was associated with a recovery of LGE in a new scintigraphic study 7 weeks later (Table 1). The patient achieved a negative sputum culture for the first time (Figure 1) and completed the induction phase with > 60 doses.

Subsequently, the treatment consolidation phase began with INH 300 mg/ RMP 600 mg/d given orally and suspending the i.v. compounds. However, a week after restarting RMP/INH, vomiting reappeared, so both drugs were suspended, and meropenem, linezolid, and i.v. levofloxacin were started again from week 21. Parenteral RMP and INH were obtained from the National Tuberculosis Control Program and applied sequentially without adverse events during the initial i.v. RMP phase. On the fifth day of INH re-exposure, vomiting was reactivated, and a new scintigraphy was performed (week 30, Table 1), which revealed a new deterioration of LGE. After a definitive INH suspension, the patient progressed in stable condition with infrequent vomiting only at evening, and therapy with ethambutol plus oral rifampin was continued in the morning to avoid loss due to emesis. Sputum cultures again became positive for *M. tuberculosis* from week 28 onwards (Figure 1). He was discharged after 35 weeks of hospitalization, with instructions to continue treatment in a Primary Healthcare Center. Subsequently, the patient

Table 1. Solid and liquid gastric emptying during different treatment phases with antituberculous drugs, in a patient with secondary gastroparesis to INH

Week since admission and gastric emptying (GE) study	Drug use and clinical condition	Higher retention site	GE Deterioration level	GE measure*	Accumulated INH therapy
Week 14 Liquid GE (LGE)	Basal, Gastric Retention Syndrome	Gastric fundus	Moderate to severe	MET 26 min (reference value < 19 min)	3 months
Solid GE (SGE)		Gastric fundus		Retention at 4 h 41% (reference ≤ 10%)	
Week 21 Liquid GE	> 1 month of INH suspension plus levosulpiride	LGE: Body and antrum	Improvement	MET 16 min (normal)	Suspended for more than one month
Solid GE	Reduced vomiting	SGE: Gastric fundus	No improvement	Retention a 4 h 38% (reference ≤ 10%)	
Week 30 Liquid GE	INH re-exposition Levosulpiride therapy	Gastric fundus	Moderate to severe	MET 26 min (reference value < 19 min)	6 days after re-exposition to i.v. INH
Solid GE	Vomiting reappears	No retention	Normal	Retention at 4 h 8% (reference ≤ 10%)	

*:Reference values were taken from the literature[5] and based on the work of the American Society of Nuclear Medicine and the American Society of Neurogastroenterology and Motility. For solid gastric emptying, the food was standardized according to protocol, marked with non-absorbable Tc99m sulfide colloid, and ingested in less than 10 minutes. Static images were taken in anterior and posterior projections at 0, 1, 2, 3 and 4 hours, with patient in upright position. Geometric average processing of decay-corrected stomach counts was plotted, with a linear fit plot with retention percentages. Normal solid gastric emptying values are: ≤ 90% at 1 h, ≤ 60% at 2 h, ≤ 30% at 3 h and ≤ 10% at 4 h. Liquid emptying was standardized according to protocol, with 300 ml of radioactive water labeled with non-absorbable Tc99m DTPA. Dynamic images were taken in left anterior oblique projection for 30 minutes with the patient in a semi-sitting position. For processing, mean emptying time (MET) values were obtained from the exponential fitting curve of the decay-corrected stomach counts/time plot. Normal value: <19 min (2 SD), < 22 min (3 SD).

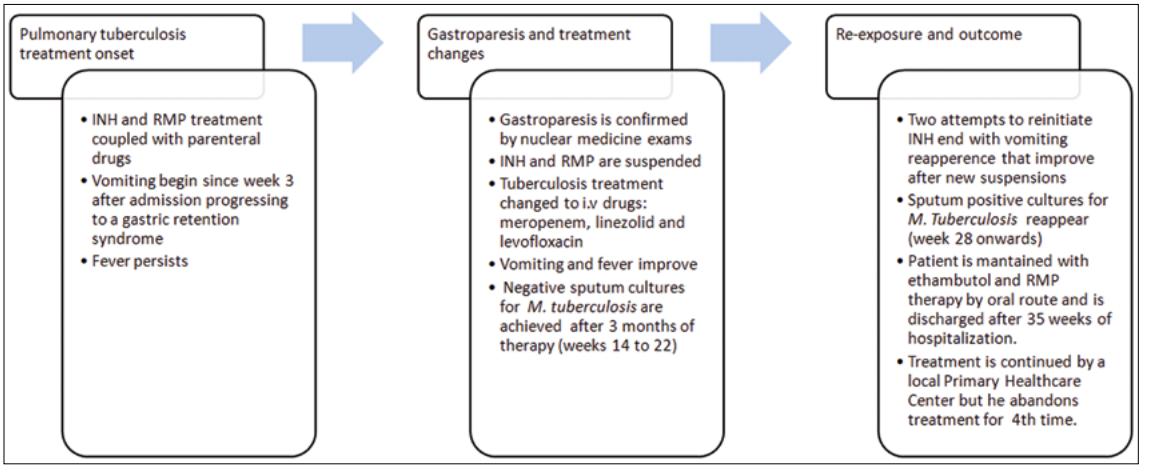

Figure 1.

again abandoned anti-tuberculosis treatment, and his current situation is unknown.

Discussion

We believe that the causality of gastroparesis due to INH is well documented by the temporality of the events, improvement with the suspension of the suspected drug, reappearance of symptoms with re-exposure on several occasions, absence of other plausible causes, and a compatible laboratory measurement. According to the WHO and Karch-Lasagna criteria, this is a definitive adverse effect[6,7]. We did not find a similar case in the literature and only indirect evidence in animal studies where after the intraperitoneal INH administration two times per week for 5-20 doses, histological neurotoxicity was demonstrated in the mesenteric plexus[8]. Additionally, exposures to INH during previous treatment, doses > 5 mg/kg body weight, alcoholism, and malnutrition may have contributed to this damage despite pyridoxine supplementation. The patient appears to have been left with permanent partial damage marked by the presence of evening vomiting. We can reasonably rule out the consumption of *Cannabis sativa* as a cause of his vomiting and gastric retention[9] since the condition began lately after admission and presented evident variations in relation to exposure to isoniazid.

We suspected a gastric retention syndrome by the presence of large-volume vomiting of low frequency and distanced from ingestion. This syndrome indicates the permanence of food or liquids in the stomach beyond 8 to 12 hours of feeding. It is associated with multiple functional or mechanic pathologies localized from the stomach to the angle of Treitz. These causes include obstructive anthro-pyloric or duodenal lesions or functional alterations, including gastroparesis[10]. The first were discarded by endoscopic studies, so we concluded that a functional disorder should be involved.

Gastroparesis is a chronic symptomatic disorder characterized by delayed gastric emptying without mechanical obstruction (> 10% food retention at 4 hours)[11].

Scintigraphy is the most cost-effective, simple, and widely available technique to confirm the presence of delayed gastric emptying. In this case, gastroparesis was documented with gastric emptying scintigraphies for solids and liquids using standardized protocols[5]. The leading causes of delayed gastric emptying are endocrine, neurological, or metabolic etiology. Diabetic gastroparesis is the primary clinical entity with a cumulative incidence of 5% and 1% for Diabetes mellitus type 1 and 2, respectively, in population cohort studies, and higher than the 0.2% observed in a control population[12]. INH could induce a critical deficiency of GABA at the mesenteric level, an inhibitory neurotransmitter that modifies or suppresses excitatory neurons at the level of

the gastric smooth muscle. After the first stage of ascending contraction above the level of luminal stimulation for the passage of the food bolus, a second stage of descending inhibition is needed below the level of distention so that the gastric content encounters a minimum of resistance to flow. This second stage is mediated by GABA and other neurotransmitters[12]. Although it is not possible to establish the exact mechanism by which gastroparesis was caused in our patient, it is attractive to propose a local GABA deficiency as its cause.

Numerous drugs and endoscopic procedures have been evaluated for the management of gastroparesis with variable results. These include prokinetics such as dopamine 2 receptor (D2) antagonists that cross (metoclopramide, clebopride) or do not cross the blood-brain barrier (domperidone), serotonin receptor agonists, motilin-like agents (macrolides), and ghrelin receptor agonists. Antiemetic or neuromodulatory drugs such as levosulpiride can also be used. They all accelerate gastric emptying, but compared to placebo, their efficacy is not always evident[13,14]. D2 antagonists are superior as class molecules. However, only some drugs (i.e., levosulpiride) have been analyzed in a systematic review[13,14] Levosulpiride promotes gastric emptying as a selective antagonist of the dopamine D2 receptor[14,15].

Gastroparesis generated an intense and prolonged morbidity and prevented microbiological control. Acid-fast bacilli and Koch cultures remained positive in sputum beyond the third or fourth month after treatment started, reflecting treatment failure but without antimicrobial resistance.

The use of parenteral drugs to manage tuberculosis can be considered in case of antimicrobial resistance, adverse effects, contraindication by organ dysfunction, or absorption problems. Fluoroquinolones are considered second-line drugs, and linezolid is applied in cases of MDR or XDR strains. Meropenem is considered a complementary drug, ideally accompanied by clavulanic acid. Its usefulness was demonstrated in our patient since the combined use of these three drugs allowed a temporary microbiological control during their use[16-20].

INH-associated gastroparesis should be added to the list of isoniazid-associated adverse effects, even in patients receiving pyridoxine supplementation. Its recognition is clinically suspected; it can be confirmed with nuclear medicine studies and affects the eradication of *M. tuberculosis*.

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