Esomeprazole-Induced Central Fever with Severe Myalgia

Ignazio Grattagliano, Piero Portincasa, Mauro Mastronardi, Vincenzo O Palmieri, and Giuseppe Palasciano

OBJECTIVE: To report a case of central fever associated with severe myalgia following esomeprazole.

CASE SUMMARY: A 64-year-old man presented with intense cephalalgia; severe, diffuse myalgia; and fever (>40 °C) after esomeprazole initiation for treatment of gastritis. Five hours after ingestion of the first esomeprazole pill (40 mg), the patient developed fever associated with cephalalgia and myalgia. This condition lasted about 40 hours and disappeared spontaneously. Symptoms partially responded to acetaminophen. Four days later, the patient received a second dose of esomeprazole 40 mg. Subsequently, 4 hours later, fever (>40 °C), headache, and difficulty in the movement of all parts of the body recurred. Neurologic examination was negative except for a minor state of disorientation. All reflexes were normal or slightly decreased. No skin lesions or breathing difficulty was noted. Routine blood tests were normal. Again, symptoms resolved spontaneously about 40 hours later.

DISCUSSION: The temporal connection between esomeprazole intake and the onset of fever suggests a probable causal link, as confirmed by the Naranjo probability scale. However, the pathogenic mechanism remains unclear. Considering that esomeprazole is able to cross the blood–brain barrier, its peak serum concentration is reached 90–180 minutes after oral administration, and its serum half-life is approximately 2 hours, we assume that the appearance of fever with accompanying neurologic and muscular symptoms might result from the drug interference with the hypothalamic regulatory center of body temperature.

CONCLUSIONS: Hyperpyrexia of central origin associated with intense cephalalgia and myalgia may occur as an adverse effect of esomeprazole therapy.

KEY WORDS: central fever, esomeprazole, headache, hyperpyrexia, myalgia, proton-pump inhibitors.

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Esomeprazole, the optical *S*-isomer of omeprazole, inhibits gastric acid secretion by blocking the hydrogen–potassium–ATPase enzyme at the surface of the gastric parietal cells. Given in a dose of 40 mg, esomeprazole is more effective in reducing gastric acid secretion than other proton-pump inhibitors (PPIs) at equimolar doses.[1] Notwithstanding the large use of PPIs, severe cerebral adverse effects have been rarely described with these medications. However, while it is not infrequent to see a patient with intolerable headache or dizziness following use of a PPI,[2] the simultaneous occurrence of cephalalgia, myalgia, and fever, as of this writing, has never been described. We report a case of these symptoms after use of esomeprazole.

Author information provided at the end of the text.

Case Report

A 64-year-old man working as an electrician arrived at the outpatient clinic with intense cephalalgia, severe and diffuse myalgia, and fever (>40 °C) that developed a few hours after starting esomeprazole 40 mg. The patient's medical history was negative for major hepatic, cardiac, pulmonary, and renal diseases. His history of drug intake disclosed only the use of nonsteroidal antiinflammatory drugs for sporadic back pains, no more than 2–3 times per year, with the last intake 3 months earlier. In October 2003, because of epigastric pain in the fasting state and abdominal tension during the postprandial period, the patient underwent a ^{13}C-urea breath test, which confirmed a *Helicobacter pylori* infection. A standard eradication triple regimen was started with esomeprazole 20 mg twice daily, clarithromycin 500 mg twice daily, and amoxicillin 1 g twice daily for one week without complaints. This therapy successfully eradicated *H. pylori*, as confirmed by a negative ^{13}C-urea breath test 2 months later.

The patient was seen again in April 2004, when gastrointestinal symptoms recurred. On this occasion, he received pantoprazole 40 mg/day for 3 weeks without adverse events and with improvement in the discomfort. However, the symptoms recurred and treatment was suspended. One

month later, an upper endoscopy was performed and revealed chronic gastritis with multiple erosions in the antrum. The lesions were biopsied, and histology demonstrated the presence of areas of intestinal metaplasia but no *H. pylori* colonies. According to clinical, endoscopic, and histologic features, esomeprazole 40 mg/day was taken 30 minutes before breakfast for 4 weeks. Five hours after ingestion of the first pill, the patient developed fever (>40 °C) preceded by shivering and associated with intense headache and diffuse myalgia; he decided to stop esomeprazole. All symptoms lasted approximately 40 hours, disappearing completely in the evening of the next day. On that occasion, symptoms were ascribed to a flu-like picture; acetaminophen 1 g was administered 2 hours and again 4 and 10 hours after the appearance of the fever with only a partial response, since body temperature remained invariably >38.5 °C (serial measurements starting 1 h after acetaminophen administration).

Four days later, the patient was again asked to take esomeprazole 40 mg. However, after 4 hours, fever (>40 °C) occurred again and was accompanied by intense and diffuse headache with difficulty in the movement of joints and muscles (including eyelids and lips). Neurologic examination was negative except for minor disorientation; reflexes were normal or slightly decreased. There were no skin lesions, liver enlargement, or breathing difficulties. Esomeprazole was stopped and acetaminophen given with the same modalities as before, which attenuated the symptoms only slightly. The patient denied previous hospitalization as well as any other therapy. The clinical picture progressively improved, and signs and symptoms disappeared spontaneously after approximately 40 hours. At this time, the clinical diagnosis of an adverse drug reaction was suspected. Results of a complete set of blood tests were normal, including complete blood cell count, erythrocyte sedimentation rate, alanine aminotransferase, creatine kinase, and myoglobinemia. The office for the surveillance of drug-related adverse effects by the Italian Ministry of Health (Rome) was promptly informed through a written communication. During the 6 months of follow-up, the patient has not been taking any medication and has had no illness.

Discussion

Fever is one of the most common adverse events during drug intake.[3] Generally, it is triggered by a hypersensitivity reaction and is associated with characteristic signs and symptoms (eg, skin rashes, nettlerash, purpura, edema, bronchospasm). This picture was absent in our patient, and he had no prior history for allergies to drugs or other substances. He was otherwise healthy and was not taking any other medication at the time of esomeprazole therapy.

According to the esomeprazole package insert,[4] fever, cephalalgia, and myalgia are possible, although rare and independent adverse events. A MEDLINE search (1990–July 2004) using the terms fever, myalgia, adverse drug reaction, esomeprazole, and/or PPIs failed to find relevant publications. PPI-associated hyperpyrexia is mainly described within a hypersensitivity reaction.[5,6] Either myalgia[7,8] or headache[9-12] is more frequently described, ranging from 3% to 30% of the patients taking PPIs.[10,12] In one case, omeprazole was associated with the onset of delirious psychosis, which completely disappeared after treatment discontinuation.[13]

In this respect, the present case report is original, since there was a probable causal temporal relationship between fever and esomeprazole use, as confirmed by a positive objective causality assessment.[14] At this time, the ultimate pathogenic mechanism of the described adverse effects remains unclear. It could be argued that esomeprazole interferes with some hypothalamic centers, including the one involved in regulating body temperature. This hypothesis is supported by at least 3 considerations. First, esomeprazole, but not all of the other PPIs, crosses the blood–brain barrier.[15] Second, the bioavailability of oral esomeprazole results in a peak serum concentration after 90–180 minutes from ingestion, with a serum half-life estimated to be about 2 hours; such pharmacokinetic characteristics are consistent with the appearance of the reactions and not in contrast with the time of their disappearance. Finally, the intrinsic metabolic clearance of esomeprazole results in higher plasma concentrations and enhanced tissue delivery compared with other PPIs, but not pantoprazole. Taken together, such considerations may account for the simultaneous appearance of hyperpyrexia, headache, and muscular pain in our patient. In this respect, omeprazole in experimental conditions has been shown to interfere with certain brain enzymes and functions and inhibit both carbonic anhydrase activity and cerebrospinal fluid formation; these actions may be translated to its isomer, esomeprazole.[16,17]

Since adverse effects occurred with esomeprazole 40 mg, but not with lower doses or with other PPIs, we speculate that the adverse events that our patient developed were rather drug-specific and dose-dependent and not triggered by a hypersensitivity-like syndrome. Hypersensitivity reactions, in fact, generally occur after the second or third contact with the allergenic substance, and chemical analogs can also trigger the immunologic event. In our case, the patient had already taken esomeprazole 20 mg a few months earlier and pantoprazole 40 mg some weeks before without appearance of adverse effects. Moreover, he did not present with the hallmark symptoms that are characteristic of a hypersensitivity reaction.

Until now, pharmacodynamic mechanisms explaining the appearance of adverse reactions at the cerebral level after PPIs have neither been described nor realistically proposed. Thus, assumptions and comments concerning the present case report remain rather speculative. In our opinion, this was a dose-related event, since esomeprazole 20 mg twice daily for 7 days did not evoke such effects. Accordingly, the reaction might be explained by considering that 40 mg of esomeprazole given in one dose results in a higher plasma concentration than 2 administrations 12 hours apart; therefore, a much higher amount of the compound per time/unit could likely cross the blood–brain barrier and react with brain structures. Even equimolar pantoprazole 40 mg once daily for 3 weeks was uneventful, although the tertiary structure of esomeprazole and pantoprazole is very similar. Minor stoichiometric differences between esomeprazole and pantoprazole, however, may indeed determine a different ability to pass the blood–brain barrier and/or to bind specific sites. Also at variance with esomeprazole, pantoprazole is a mixture of both racemic forms (ie, right and left isomers); this difference might hypothetically result in a fewer number of brain receptors bound by equimolar pantoprazole. Stoichiometric differences between these 2 drugs are also responsible for differing hepatic clearance, serum concentrations, tissue delivery, and receptor binding capacity.[18,19] In this respect, the rationale for developing single drug isomers is based on

the fact that enzymes and receptors generally have a stereochemical preference for one optical isomer. This may result, in turn, in important pharmacodynamic and pharmacokinetic differences and clinical efficacy.[20]

We feel that the arguments proposed in this case report are also of clinical relevance. Whereas it is logical to consider other PPIs in this condition even if potentially risky, it is a fact that lower dosages of esomeprazole might be safer in this patient.

Conclusions

Hyperpyrexia of central origin associated with intense cephalalgia and myalgia may occur simultaneously as an adverse effect of esomeprazole 40-mg therapy. This case documents a new and unexpected event occurring after esomeprazole intake. In our opinion, although it could be considered as an unusual adverse event, this case report certainly contributes to expanding the knowledge of PPI-induced adverse reactions.

Ignazio Grattagliano MD, Clinical Specialist—Research Advisor, Section of Internal Medicine, Department of Internal Medicine and Public Medicine, University Medical School of Bari, Bari, Italy

Piero Portincasa MD PhD, Associate Professor of Internal Medicine, Section of Internal Medicine, Department of Internal Medicine and Public Medicine, University Medical School of Bari

Mauro Mastronardi MD, Clinical Specialist, Endoscopic Service, Casa di Cura "Salus," Brindisi, Italy

Vincenzo O Palmieri MD, Associate Professor of Internal Medicine, Section of Internal Medicine, Department of Internal Medicine and Public Medicine, University Medical School of Bari

Giuseppe Palasciano MD, Professor of Internal Medicine—Director, Section of Internal Medicine, Department of Internal Medicine and Public Medicine, University Medical School of Bari

Reprints: Dr. Grattagliano, Section of Internal Medicine, Department of Internal Medicine and Public Medicine, University Medical School of Bari, 70124 Bari, Italy, fax 39-080-5478232, i.grattagliano@semeiotica.uniba.it

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EXRACTO

OBJETIVO: Informar un caso de fiebre central relacionado con mialgia severa después del uso del esomeprazol.

RESUMEN DEL CASO: Un hombre de mediana edad se presentó con cefalalgia severa, mialgia difusa, y fiebre (>40 °C) después de iniciar un tratamiento para la gastritis. Cinco horas después de la ingestión de la primera dosis de 40 mg del esomeprazol, el paciente desarrolló fiebre (>40 °C) además de cefalalgia y mialgia. Esta condición duró cerca de 40 horas y desapareció espontáneamente. Los síntomas respondieron parcialmente al acetaminofén. Cuatro días más tarde, el paciente recibió la segunda dosis de 40 mg del esomeprazol. Subsiguientemente, 4 horas más tarde, recurrió la fiebre (>40 °C), el dolor de cabeza, y la dificultad en el movimiento de todas las partes del cuerpo. Un examen neurológico fue negativo, excepto por un estado de desorientación leve. Todos los reflejos estaban normales. No había presencia de lesiones de la piel ni de dificultad para respirar. Las pruebas de sangre de rutina estaban normales. Nuevamente, los síntomas desaparecieron espontáneamente cerca de 40 horas más tarde.

DISCUSIÓN: La conexión entre el tiempo de la ingestión del esomeprazol y el inicio de la fiebre indica una relación causal, según se confirma por la puntuación de una evaluación positiva de causalidad (escala de Naranjo de reacciones adversas a medicamentos). Sin embargo, el mecanismo de patogénesis permanece sin esclarecer. Tomando en cuenta que el esomeprazol puede cruzar la barrera cefalorraquídea, la concentración máxima en plasma se alcanza en 90–180 minutos después de la administración oral y la vida media sérica es de aproximadamente 2 horas, presumimos que la aparición de la fiebre con síntomas neurológicos y musculares pudieran estar relacionados con la interferencia de medicamentos con el centro regulador hipotalámico de la temperatura.

CONCLUSIONES: La terapia con esomeprazol pudiera causar un efecto adverso que se caracteriza por hiperpirexia de origen central, cefalalgia severa, y mialgia.

Rafaela Mena

RÉSUMÉ

OBJECTIF: Rapporter un cas de fièvre d'origine centrale associée à une céphalée et une myalgie sévères secondaires à l'utilisation d'esomeprazole.

RÉSUMÉ: Un home d'âge moyen présenta une céphalée intense, une myalgie diffuse, et de la fièvre (>40 °C) 5 heures après avoir ingéré un premier comprimé (40 mg) d'esomeprazole pour le traitement d'une gastrite. La condition a persisté pendant environ 40 heures pour ensuite disparaître spontanément. Les symptômes ont partiellement répondu à l'administration d'acétaminophène. Quatre jours plus tard, le patient a reçu une deuxième dose de 40 mg d'esomeprazole. Quatre heures plus tard, la fièvre (>40 °C), les maux de tête, et les douleurs musculaires sont réapparus. L'examen neurologique s'est révélé négatif sauf pour une légère désorientation. Tous les réflexes étaient normaux ou légèrement diminués. Aucune lésion cutanée ou difficulté respiratoire n'ont été observées. Les tests sanguins de routine étaient négatifs. Les symptômes ont disparu spontanément environ 40 heures plus tard.

DISCUSSION: La relation temporelle entre l'ingestion d'esomeprazole et la fièvre suggère un lien de cause à effet tel que confirmé par un score positif de l'évaluation du lien de causalité (diagramme de Naranjo). Cependant, le mécanisme pathogénique demeure incertain. Considérant que l'esomeprazole peut traverser la barrière hémo-encéphalique, que sa concentration maximale est atteinte en 90 à 180 minutes après administration orale, et que sa demie vie plasmatique est d'environ 2 heures, une possible interférence du médicament avec le centre hypothalamique régulateur de la température corporelle est suggérée.

CONCLUSIONS: Une pyrexie d'origine centrale associée à une céphalée intense et de la myalgie peut survenir suite à l'administration d'esomeprazole.

Suzanne Laplante