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Case Series

Novel Therapeutic Approach Using Proton Pump Inhibitor and Antiemetic Combination for Refractory Fever and Headache: A Case Series

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Abstract

Delayed gastric emptying during acute illness may prevent adequate medication absorption, causing therapeutic failure. We present three cases of refractory fever and headache that responded rapidly to proton pump inhibitor and antiemetic combinations. A 60-year-old female with severe headache unresponsive to paracetamol and mefenamic acid experienced complete relief 15 minutes after receiving pantoprazole 40mg with domperidone 30mg. A six-year-old with fever persisting at 101°F despite ibuprofen achieved defervescence within 20 minutes of lansoprazole 15mg with ondansetron 0.15mg/kg. A two-year-old with febrile seizure and persistent fever at 102°F unresponsive to combination antipyretics normalized temperature within 15 minutes of lansoprazole 15mg with ondansetron 0.15mg/kg. We hypothesize that acute illness induces transient gastroparesis impairing drug absorption, and that PPI-antiemetic combinations restore gastric function allowing absorption of previously administered but unabsorbed medications. This warrants controlled investigation.

Keywords: *Antiemetic Therapy, Drug Absorption, Febrile Seizure, Gastroparesis, Headache Management, Medication Malabsorption, Proton Pump Inhibitor*

Introduction

Fever and headache rank among the most frequent complaints managed in clinical practice, treated with oral antipyretics and analgesics [1]. Yet a proportion of patients fail to respond adequately to standard therapy, presenting both diagnostic and therapeutic dilemmas. While medication failure is typically attributed to inadequate dosing or drug resistance, the possibility of impaired gastrointestinal absorption deserves greater attention.

Gastroparesis, characterized by delayed gastric emptying without mechanical obstruction, affects roughly two to four percent of the general population and becomes significantly more common during acute illness [2,3]. Studies examining patients during fever or migraine demonstrate that gastric stasis substantially delays medication absorption [4,5]. Experimental evidence shows fever can increase gastric emptying time from 55 plus or minus 22 minutes to 118 plus or minus 54 minutes [6].

Since paracetamol and other antipyretics depend critically on gastric emptying for absorption in the small intestine, any delay in stomach emptying means these drugs accumulate before absorption occurs [7,8].

This delays peak plasma concentrations and reduces clinical effectiveness [9]. The migraine-gastroparesis link is well-established; studies document delayed gastric emptying in 78-80 percent of migraine sufferers during attacks [10,11].

Proton pump inhibitors (PPIs) work primarily by suppressing gastric acid but may influence motility through other mechanisms [12]. Domperidone, acting as a peripheral dopamine D2 receptor antagonist, enhances gastric contractions [13,14]. Ondansetron, a 5-HT3 antagonist, primarily works as an antiemetic but may support gastric function indirectly [15].

This case series presents three cases showing rapid resolution of refractory fever or headache after PPI-antiemetic combination therapy. The observations suggest acute illness-induced gastroparesis may explain medication failure, and that restoring gastric function allows absorption of previously unabsorbed drugs.

Case Presentation

Table 1 summarizes the key clinical features of the three cases presented in this series.

Table 1: Clinical Summary of Cases.

Case	Age/Weight	Presentation	Initial Medication	PPI-Antiemetic	Response Time
1	60-year-old female	Severe refractory headache × 3-4 hours	Paracetamol 500mg (3-4 hrs prior) Mefenamic acid 500mg (1 hr prior)	Pantoprazole 40mg + Domperidone 30mg	15 minutes
2	6-year-old, 18kg	Fever 101°F × 4 hours (minimal response: 100°F after 4 hrs)	Ibuprofen 10mg/kg (~180mg) 4 hrs prior	Lansoprazole 15mg + Ondansetron 0.15mg/kg	20 minutes
3	2-year-old, 12kg	Fever 102°F, vomiting, febrile seizure (minimal response: 100.8°F after 2 hrs)	Ibuprofen 10mg/kg + Paracetamol combination	Lansoprazole 15mg + Ondansetron 0.15mg/kg	15 minutes

Table 1 Summary: All three cases demonstrated complete symptom resolution within 15-20 minutes of PPI-antiemetic combination therapy, despite inadequate response to prior antipyretic or analgesic administration. The rapid response suggests restoration of gastric emptying enabling absorption of previously administered medications.

Case 1: Refractory headache in adult female

A 60-year-old woman presented with acute severe headache lasting three to four hours. The pain was bilateral, constant, and described as splitting in character. The patient had family history of migraine but no personal history of migraine with aura. She experienced no visual disturbances, nausea, vomiting, or other typical migraine features.

The patient had no significant medical history and took no regular medications. She had eaten lightly two to three hours before evaluation. Vital signs showed blood pressure 130/82 mmHg, pulse 78/minute, temperature 36.8 Celsius. Examination revealed photophobia and phonophobia but was otherwise unremarkable.

Prior to presentation, the patient had self-administered paracetamol 500mg approximately three to four hours earlier without relief. She then took mefenamic acid 500mg at least one hour before medical evaluation, again with no improvement. The persistent headache despite two different analgesics raised suspicion for delayed gastric absorption.

Treatment was initiated with pantoprazole 40mg combined with domperidone 30mg (Pan-D), administered orally. The patient reported complete resolution of her headache within 15 minutes of administration. No adverse effects were observed. The patient remained symptom-free at 48-hour follow-up.

This case suggests that acute headache, even without nausea or other gastroparesis signs, may involve delayed gastric emptying preventing medication absorption. The rapid response after PPI-antiemetic treatment supports the hypothesis that restoring gastric motility enabled absorption of previously administered but unabsorbed medications.

Case 2: Persistent fever in school-age child

A six-year-old boy weighing approximately 18kg presented with fever lasting four hours along with mild cough and cold. Initial temperature was 101°F (38.3°C). The child had no significant medical history, was fully vaccinated, and had never experienced febrile seizures.

The parents had administered ibuprofen 10mg/kg (about 180mg) orally four hours prior to presentation. Despite appropriate dosing, temperature dropped only minimally to 100°F (37.8°C) over the next four hours. The child remained uncomfortable and febrile. Throat examination showed erythema typical of upper respiratory infection but otherwise examination was normal.

The poor response to properly dosed ibuprofen prompted consideration of possible malabsorption. The patient reported no nausea, vomiting, or GI symptoms, making unrecognized gastroparesis a consideration.

Treatment consisted of lansoprazole 15mg plus ondansetron 0.15mg/kg (approximately 3mg) administered orally. Within 20 minutes the child's temperature normalized and he became playful and comfortable. Fever did not recur during 24-hour follow-up. The upper respiratory symptoms resolved gradually over the subsequent two to three days with supportive care.

This case demonstrates that fever itself, especially with infectious illness, can cause sufficient gastroparesis to prevent antipyretic absorption. The rapid defervescence after combination therapy suggests the previously administered ibuprofen was finally absorbed once stomach function improved.

Case 3: Febrile seizure with refractory fever in toddler

A two-year-old boy weighing 12kg presented with fever, vomiting, and one episode of febrile seizure. The seizure was generalized tonic-clonic, lasted about one minute, and was followed by 15 minutes of postictal drowsiness. This was the child's first seizure. After recovery, the child remained febrile.

Initial temperature was 102°F (38.9°C). The parents had administered Ibugesic Plus syrup (ibuprofen 100mg/5ml plus paracetamol 162.5mg/5ml) at appropriate dosing. Despite using two antipyretics together, temperature barely dropped from 102°F to 100.8°F (38.2°C) over two hours and the child remained irritable and uncomfortable.

Examination showed alertness without focal neurological deficits. Meningeal signs were absent. Throat examination showed mild erythema. The child had experienced one episode of non-bilious vomiting prior to the seizure. Laboratory investigations including complete blood count and C-reactive protein were within normal limits, ruling out serious bacterial infection.

Treatment with lansoprazole 15mg combined with ondansetron 0.15mg/kg (approximately 2mg) was administered orally. Fifteen minutes later the child's temperature normalized to 98.6°F (37°C).

The child became comfortable, playful, and began feeding well. No further seizures occurred and fever did not recur during 72-hour follow-up.

This case demonstrates that gastroparesis can develop during febrile seizure, complicating both seizure control and fever management. The rapid response to combination therapy restored fever control and likely reduced seizure recurrence risk.

Discussion

The central hypothesis of this case series is that acute illness—whether from fever or pain—triggers temporary gastroparesis that blocks oral drug absorption. PPI-antiemetic combinations may restore stomach function and permit absorption of medications already taken but sitting unabsorbed in the stomach.

Strong evidence supports illness-induced gastroparesis. Research shows fever increases gastric emptying time from 55 plus or minus 22 to 118 plus or minus 54 minutes [6]. The mechanism involves multiple factors including inflammatory mediators like interleukin-1, interleukin-6, and tumor necrosis factor released during illness. These cytokines directly interfere with vagal nerve signaling and reduce stomach muscle contraction [16].

The migraine-gastroparesis connection is especially well-documented. Scintigraphy studies show delayed gastric emptying in 78-80 percent of migraine patients during attacks [10,11]. The literature emphasizes that stomach stasis delays medication absorption and reduces peak blood levels and clinical benefit. This explains why the first patient obtained no relief from two different oral analgesics.

Exactly how PPI-antiemetic combinations work to restore gastric function deserves examination. PPIs do not sit in the traditional prokinetic category, yet they may influence motility through multiple paths. By raising stomach pH, they may help with food breakdown and reduce the emptying delay that comes from incomplete digestion. Some research suggests PPIs act directly on muscle cells independent of acid suppression, though this remains debated [12].

Domperidone's prokinetic action is well-proven. As a dopamine D2 receptor antagonist in the periphery, it blocks inhibitory dopamine signaling on stomach muscle and enhances acetylcholine activity [13,14]. Studies show it lowers stomach residual volume and speeds emptying within two hours [17]. Critically, it does not easily cross the blood-brain barrier, so it helps stomach motility without central nervous system effects [18].

Ondansetron works differently. As a 5-HT3 antagonist, its primary role is antiemetic—blocking serotonin in the chemoreceptor trigger zone and vagal fibers [15]. Studies on its stomach emptying effects show mixed results, with some showing no effect on solid emptying [19] while others report context-dependent effects. However, its strong anti-nausea power may indirectly support gastric function by stopping nausea-driven stomach paralysis and letting normal patterns resume [20].

The fast symptom relief (15-20 minutes) most likely comes from suddenly absorbing previously stuck medications. When paracetamol reaches the small intestine, it peaks in blood within 20-90 minutes depending on stomach emptying [7,8]. Ibuprofen and mefenamic acid show similar absorption patterns [9]. If these drugs sat unabsorbed in the stomach from gastroparesis, restoring stomach function would quickly move them to the intestine for absorption—explaining the prompt relief.

Alternative mechanisms deserve consideration. PPIs show anti-inflammatory properties beyond acid suppression that could directly influence pain or fever pathways [12]. Both gastroparesis and migraine involve vagal dysfunction, and domperidone might indirectly modulate vagal tone to address both stomach problems and pain [11]. Ondansetron's serotonin blocking affects multiple systems beyond nausea and may influence pain and fever independently. The gut-brain axis involves extensive serotonin signaling linking stomach, pain perception, and temperature control [4,5].

Could these drugs themselves treat the symptoms? Unlikely. Their known mechanisms do not primarily include antipyretic or pain-relief actions. The speed of response (15-20 minutes) exceeds what would be expected for new drug absorption and distribution. Standard doses were used, not high therapeutic doses for pain or fever.

The placebo effect cannot fully explain these results. The same evidence-based antipyretics that failed initially also carry placebo benefit, yet they did not work. Consistent rapid response was observed across three different patients with different conditions. The febrile cases showed objective temperature drops. The biologic plausibility of the gastroparesis mechanism is strong.

Pediatric patients present special considerations. Children have more variable gastric emptying, less acidic stomach pH, and different drug metabolism than adults [13,14]. These factors may make children more prone to absorption problems during acute illness. Children also mount stronger fever responses, potentially causing greater stomach dysfunction.

The clinical implications are significant if confirmed through larger study. This approach could offer rapid, safe, inexpensive intervention for refractory fever or headache before resorting to injected drugs. The medications used here have excellent safety track records. PPIs are among the world's most prescribed drugs with generally good tolerability. Short-term domperidone at standard doses is generally safe, though high doses raise QT concerns in certain patients [17]. Ondansetron is widely used in children for nausea with good safety data [15].

Certain groups need careful consideration. Domperidone requires caution in patients with heart arrhythmias, serious heart disease, or electrolyte problems, particularly elderly patients [17]. PPIs can interact with drugs that need acidic stomachs for absorption. In children, age-proper dosing and formulations matter.

Rapid response should never skip proper diagnosis. In the febrile seizure case, investigation ruled out serious infection before attributing symptoms to gastroparesis. Severe headaches need consideration for serious brain problems. Persistent fever might signal infection needing antibiotics.

This case series shows preliminary findings requiring rigorous validation. Future work should include randomized controlled trials comparing PPI-antiemetic combinations to standard care, direct gastric emptying studies using imaging, pharmacokinetic studies measuring drug blood levels before and after intervention, and pediatric-specific trials given unique pediatric factors.

Conclusions

This case series presents a novel therapeutic approach for refractory fever and headache using PPI-antiemetic combinations. All three patients demonstrated rapid symptom resolution (15-20 minutes) without adverse effects, supporting the hypothesis that acute illness-induced gastroparesis impairs oral medication absorption and that restoring gastric function enables absorption of previously administered drugs.

These preliminary observations warrant validation through controlled clinical trials. If confirmed, this simple, safe, and cost-effective approach could provide a valuable alternative to parenteral therapy in acute care settings, potentially reducing healthcare costs and procedural distress particularly in pediatric populations.

Additional Information

Human Subjects: Consent was obtained from all patients and their guardians for publication of this case series.

Conflicts of Interest: The authors declare no conflicts of interest, financial relationships, or competing interests.

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