Buried bumper syndrome: incidence study and clinical characterization of a rare complication of percutaneous endoscopic gastrostomy

To the Editor,

Buried bumper syndrome (BBS) is a rare complication of percutaneous endoscopic gastrostomy (PEG), in which the internal fixation device migrates alongside the tract of the stoma outside the stomach, with an incidence of approximately 1% [1]. Although rare, it can be associated with severe complications including gastrointestinal bleeding, perforation or abscess and, considering the increasing number of patients requiring PEG for enteral nutrition, it may become a significant clinical problem [2].

We retrospectively analyzed every patient who performed PEG between January 2016 and December 2021 at Centro Hospitalar Universitário de São João (Porto, Portugal) and included all cases with endoscopic diagnosis of BBS. The aims of our study were to evaluate its incidence and main clinical characteristics.

A total of 9 cases of BBS were identified (Table I) in a total of 774 patients who performed PEG, which corresponds to an incidence of 1.2%. Most patients were male (n=8) and their median age was 75 years (range 29-96). Indications for PEG placement were stroke (n=2), Alzheimer's disease (n=2), Parkinson's disease (n=1), prolonged intensive care (n=1), laryngeal cancer (n=1), spinal injury (n=1) and cerebral arteriovenous malformation (n=1). PEG had been performed by the "pull" technique at anterior distal gastric body with a tube of 24 Fr (n=5) or 20 Fr (n=4). There were no immediate adverse events in any patient. The mean time interval between PEG placement and BBS was 4.8 months (range 0-23). Buried bumper syndrome occurred with semi-rigid fixation devices in 7 patients, whereas in 2 cases it occurred with balloon fixation. The most common clinical manifestations were pain (n=4), peristomal leakage (n=4), local tumefaction (n=4), inability to insert content (n=3), purulent exudate (n=2) and fever (n=1). Endoscopy revealed internal gastrostomy orifice at the anterior

Table I. Main characteristics of patients

Case	Gender	Age	PEG indication	Time PEG-BBS (months)	Clinical manifestations	Infection	2nd PEG	Time BBS-2nd PEG (weeks)	Recurrence
# 1	Male	47	Prolonged ICU stay	1	Pain, tumefaction	No	Yes	15	No
# 2	Male	84	Alzheimer's dementia	1	Inability to insert	No	No	N/A	No
# 3	Male	62	Laryngeal cancer	1	Pain	No	Yes	0	No
# 4	Female	79	Parkinson's disease	0	Peristomal reflux, pain, tumefaction	Yes	No	N/A	No
# 5	Male	96	Alzheimer's dementia	11	Peristomal reflux	No	Yes	5	No
# 6	Male	72	Stroke	4	Inability to insert, pain	Yes	No	N/A	No
# 7	Male	78	Spinal injury	23	Purulent exudent, tumefaction	Yes	Yes	5	No
# 8	Male	75	Stroke	0	Peristomal reflux, purulent exudate, tumefaction	Yes	No	N/A	No
# 9	Male	29	Cerebral arterio-venous malformation	2	Peristomal reflux, purulent exudate, fever	Yes	Yes	0	Yes

BBS: buried bumper syndrome; PEG: percutaneous endoscopic gastrostomy; ICU: intensive care unit: AVM: arteriovenous malformation.

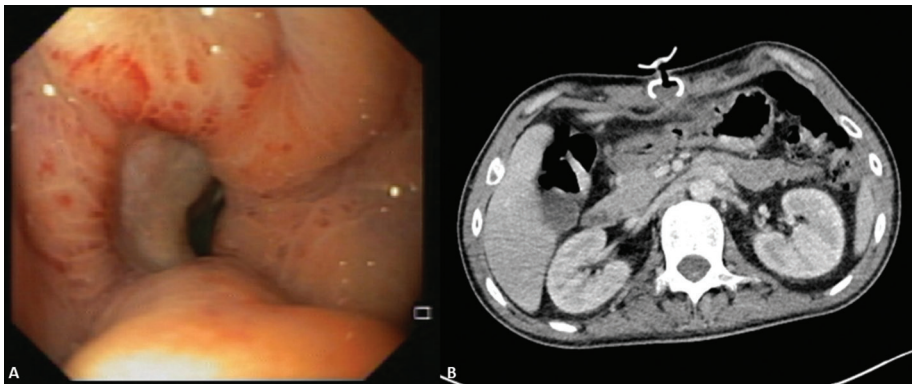

Fig. 1. A) Upper digestive endoscopy reveals the internal orifice of the stomal tract after migration of the internal bumper. B) Abdominal CT showing exteriorization of the internal bumper in the fistulous tract.

surface of the gastric body with an absence of a migrated internal fixation device (Fig. 1A), with endoscopic signs of infection in 2 patients. Imaging techniques were performed in 8 patients to confirm dislocation of the internal fixation device (Fig. 1B) and adjacent phlegmon was detected in 2 (25%). Overall, there was evidence of local infection in 5 patients and all were successfully treated with antibiotics. Two patients were anticoagulated although the therapeutic approach was not changed since no high-risk bleeding procedures were performed. Extraction of the inner bumper through the stoma tract was performed in all patients after BBS diagnosis and replaced with a second gastrostomy set in five, after mean time interval of 5 weeks. Recurrence was detected in one patient (20%), a 20-year-old male in whom PEG was placed for rupture of cerebral arteriovenous malformation and, 2 months later, presented with BBS. This was removed and immediately replaced, with recurrence of BBS 4 weeks after placement of the 2nd PEG.

Excessive compression between internal and external fixation devices is considered the main etiological factor leading to BBS and the most important preventive measure is an adequate positioning of the external bolster with a recommended distance from skin to external fixator of 10 mm. Inability to insert, loss of patency and peristomal leakage are a typical symptomatic triad [3]. Gastroscopy is indicated in all cases where BBS is suspected. The depth of disc migration in relation to the lamina muscularis propria of the stomach can be estimated by endoscopic or abdominal ultrasound and is critical to define management: a disc retained inside the stomach and completely covered by overgrowing tissue can be released using some type of endoscopic dissection technique (needle knife, argon plasma coagulation or papillotome through cannula) whereas a disc localized out of lamina muscularis should be treated by a surgeon [4]. A new gastrostomy set can be placed directly through the same stoma in most cases and the risk of recurrence is low if preventive measures are applied [5].

In conclusion, we report a low incidence of BBS (1.2%). Extraction of the inner bumper through the stoma tract and posterior placement of a new set is usually feasible. Although uncommon, recurrence may occur and the importance of taking preventive measures cannot be overemphasized.

Emanuel Dias, João Santos-Antunes, Armando Peixoto, Rosa Ramalho, Guilherme Macedo

Gastroenterology Department, Centro Hospitalar de São João, Porto, Portugal

Correspondence: Emanuel Dias, diasj0310@gmail.com

Conflicts of interest: None.
DOI: 10.15403/jgld-4483

REFERENCES

1. El AZ, Arvanitakis M, Ballarin A, Devière J, Le Moine O, Van Gossum A. Buried bumper syndrome: low incidence and safe endoscopic management. Acta Gastroenterol Belg 2011;74:312-316.
2. Biswas S, Dontukurthy S, Rosenzweig MG, Kothuru R, Abrol S. Buried bumper syndrome revisited: a rare but potentially fatal complication of PEG tube placement. Case Rep Crit Care 2014;2014:634953. doi:10.1155/2014/634953
3. Schrag SP, Sharma R, Jaik NP, et al. Complications related to percutaneous endoscopic gastrostomy (PEG) tubes. A comprehensive clinical review. J Gastrointestin Liver Dis 2007;16:407-418.
4. Cyrany J, Rejchrt S, Kopacova M, Bures J. Buried bumper syndrome: A complication of percutaneous endoscopic gastrostomy. World J Gastroenterol 2016;22:618-627. doi:10.3748/wjg.v22.i2.618
5. Zouk AN, Batra H. Managing complications of percutaneous tracheostomy and gastrostomy. J Thorac Dis 2021;13:5314-5330. doi:10.21037/jtd-19-3716

An unexpected cause of hiccups: esophageal variceal band ligation

To the Editor,

Hiccups are usual reflex conditions due to involuntary, intermittent and spasmodic contractions of intercostal muscles and the diaphragm [1]. Generally, its frequency varies from 4 to 60 hiccups per minute. Many conditions may lead to hiccups such as excessive eating, aerophagia, situations resulting in irritation of vagus and/or phrenic nerve (e.g. acid reflux) and central nervous system pathologies [2]. Persistent hiccups, which refer to hiccups lasting more than 48 hours, are rare conditions that may decrease quality of life [3].

Here we present an unusual case of hiccups following esophageal variceal band ligation (EVBL). A 68-year-old

male patient diagnosed with cirrhosis secondary to ethanol abuse was hospitalized for secondary EVBL following variceal bleeding. MELD score was 24 and Child-Pugh class C (11 points) at admission. Grade 3 esophageal varices were found at the middle esophagus extending to Z- line in endoscopy. Six bands were placed in an upward spiral motion for secondary prophylaxis (Fig. 1). Hiccups developed following the procedure. In order to evaluate possible etiologies that might have caused hiccups, laboratory tests, chest x-ray, thoracoabdominal computed tomography were obtained. The patient was consulted to neurology and otorhinolaryngology departments. There were no pathologic findings in their examinations. Chlorpromazine was initiated for symptomatic relief. However, the patient started to suffer acute mental status changes after oral administration of chlorpromazine at third day of treatment, so it was switched to metoclopramide. The patients' hiccups resolved with metoclopramide eventually and didn't recur.

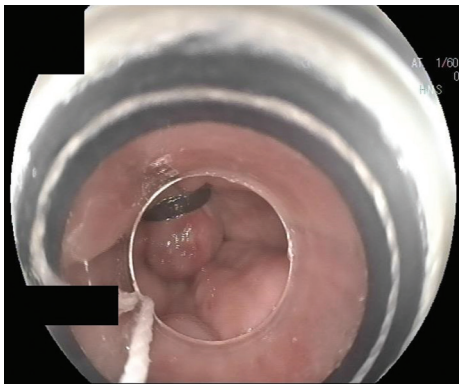

Fig. 1. Endoscopic image of EVBL procedure.

Acute hiccups may be managed with physical maneuvers. However, persistent or intractable flares may continue for days even months and can be distressing and hard to treat [2]. In our patient with persistent hiccups following EVBL, pharmacological treatment was initiated as soon as other possible etiologies were excluded. Symptomatic relief was achieved with metoclopramide. Hiccups didn't recur after cessation of medication. Although the underlying mechanism of persistent hiccups in these patients is not fully understood, it is thought to be caused by possible irritation of anatomic structures localized around surgical site. In current literature, there are cases reporting persistent hiccups following procedures such as gastric variceal band ligation and several surgical procedures [4, 5]. However, there was no case reporting hiccups following EVBL.

Merve Eren Durmuş[1], Serkan Öcal[2], Adil Duman[2], Ruhsen Öcal[3], Gökhan Köker[1]

1) Internal Medicine Department, University of Health Sciences Antalya Training and Research Hospital, Antalya; 2) Department of Gastroenterology, University of Health Sciences Antalya Training and Research Hospital, Antalya; 3) Department of Neurology, University of Health Sciences Antalya Training and Research Hospital, Antalya, Turkey

Correspondence: Merve Eren Durmuş, drmerveeren@gmail.com

Conflicts of interest: None.
DOI: 10.15403/jgld-4588

REFERENCES

1. Kahrilas PJ, Shi G. Why do we hiccup? Gut 1997;41:712-713. doi:10.1136/gut.41.5.712
2. Steger M, Schneemann M, Fox M. Systemic review: the pathogenesis and pharmacological treatment of hiccups. Aliment Pharmacol Ther 2015;42:1037-1050. doi:10.1111/apt.13374
3. Kolodzik PW, Eilers MA. Hiccups (singultus): review and approach to management. Ann Emerg Med 1991;20:565-573. doi:10.1016/s0196-0644(05)81620-8
4. Tang Y, Asthana A, Lubel J. Unusual cause of hiccup and abdominal pain after gastric variceal obliteration. Gastroenterology 2013;144:e1-e2. doi:10.1053/j.gastro.2012.08.036
5. Lee AR, Cho YW, Lee JM, Shin YJ, Han IS, Lee HK. Treatment of persistent postoperative hiccups with stellate ganglion block: Three case reports. Medicine (Baltimore) 2018;97:e13370. doi:10.1097/MD.0000000000013370

Accelerated ustekinumab dosing as rescue therapy in acute severe ulcerative colitis

To the Editor,

We report a case of acute severe ulcerative colitis (ASUC) that was successfully treated with off label accelerated dose ustekinumab monotherapy.

A 75-year-old man with underlying ischemic heart disease, congestive heart failure, diabetes, chronic obstructive pulmonary disease (COPD) presented with ASUC. He had initially presented to another physician three weeks prior with one month history of bloody diarrhea. He was diagnosed with ulcerative colitis (UC) and mesalazine 3g a day was started. However, his symptoms continued to worsen with bloody diarrhea 6 times a day, severe lethargy, and fever. On admission, his temperature was 38.2°C, pulse rate was 90 beats per minute, blood pressure was 128/68 mmHg, abdomen was soft and mildly distended. Laboratory test revealed hemoglobin 91 g/dL, albumin 23 g/L and C-reactive protein 144 mg/L. Abdominal computed tomography showed diffuse long segment bowel thickening at the rectum extending to the splenic flexure with pericolonic fat stranding (Fig. 1A). Unprepared left flexi-sigmoidoscopy showed severe inflammation with deep ulceration (Fig. 1B). Clostridioides difficile and Cytomegalovirus infection were ruled out. He was started on intravenous Hydrocortisone 100mg QID and initially had a good clinical response at day 5 with a reducing CRP to 19 mg/L. However, upon changing to prednisolone at day 8, he developed worsening of diarrhea 10 times/day and his CRP increased back to 70.89 mg/L. He was started back on intravenous steroids but still did not achieve adequate response and his diabetic control worsened. Although he was referred to the surgeons, he was deemed to be a high-risk surgical patient which he also refused. We were reluctant to start him on infliximab or cyclosporin because the patient had COPD with multiple previous admissions for infective exacerbations.

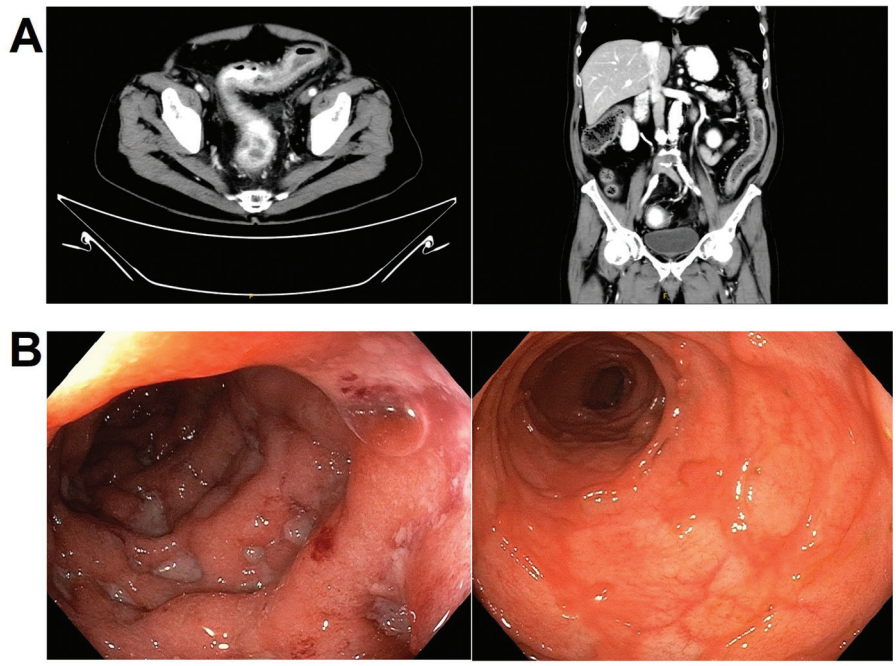

Fig. 1. A) Axial view (left) & coronal view (right) of computerized tomography abdomen showed diffuse thickening of sigmoid colon suggestive of active colitis; B) Endoscopic appearance showing severe colitis and deep ulceration during acute severe ulcerative colitis before ustekinumab therapy (left) and complete mucosa healing with pseudopolyps and scar formation after 24 weeks of ustekinumab therapy (right).

In view of this, we started him on off label ustekinumab in view of the more favorable side effect profile and relatively rapid onset of action. He was given an intravenous loading dose of 390 mg (Week 0) followed by 90mg subcutaneous dose at week 2, week 6 and then 8-weekly maintenance intervals. He clinically responded well to the treatment and repeat colonoscopy at week 24 showed complete mucosal healing with pseudopolyps and scarring (Fig. 1B).

Infliximab and cyclosporin are two well established treatments for ASUC following inadequate response to standard high dose intravenous corticosteroids. Unfortunately, even with these treatments, a large proportion of patients still require emergency colectomy [1]. Infliximab and cyclosporin also are associated with a significant risk of adverse events especially in more vulnerable groups such as older patients with multiple co-morbidities where the risk of infection and malignancy is a concern. In contrast, ustekinumab and vedolizumab have better side effect profiles.

Ustekinumab is a monoclonal antibody targeting Interleukin 12/23 that has been licensed in the treatment of moderate to severe UC; however, the use of ustekinumab as a rescue therapy in management of ASUC has not previously been described. Ustekinumab clearance is much higher in patients with low albumin levels, hence a higher dose is required to maintain the efficacy of treatment in ASUC [2]. We decided to use an accelerated 2-week interval dosing as a case series had shown that 2-weekly dosing was effective and safe [3]. Although our case highlights the potential efficacy of accelerated dose ustekinumab in inducing mucosal healing in ASUC, there is still insufficient data to support this approach as a first line rescue therapy, but rather a consideration when infliximab or cyclosporin is contraindicated or when there is a significant risk of infection in a vulnerable patient. We also hope that this will encourage more studies in the future to clarify the further role of ustekinumab in the management of ASUC.

Nik Arsyad Nik Muhamad Affendi[1,2], Choon Jin Ooi[3], Ida Normiha Hilmi[1]

1) Division of Gastroenterology and Hepatology, Department of Medicine, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia; 2) Division of Gastroenterology and Hepatology, Faculty of Medicine, International Islamic University of Malaysia, Kuantan, Malaysia; 3) Duke-NUS Medical School, Gleneagles Medical Centre, Singapore

Correspondence: Ida Normiha Hilmi,
Ida.hilmi@gmail.com, ida@ummc.edu.my

Conflicts of interest: None.
DOI: 10.15403/jgld-4599

REFERENCES

1. Laharie D, Bourreille A, Branche J, et al; Groupe d'Etudes Thérapeutiques des Affections Inflammatoires Digestives. Ciclosporin versus infliximab in patients with severe ulcerative colitis refractory to intravenous steroids: a parallel, open-label randomised controlled trial. Lancet 2012;380:1909-1915. doi:10.1016/S0140-6736(12)61084-8
2. Wang Z, Verstockt B, Sabino J, et al. Population pharmacokinetic-pharmacodynamic model-based exploration of alternative ustekinumab dosage regimens for patients with Crohn's disease. Br J Clin Pharmacol 2022;88:323-335. doi:10.1111/bcp.14971

3. Storan D, Doherty GA, Cullen G. Ustekinumab 90 mg Every 2 Weeks for the Treatment of Inflammatory Bowel Disease. Clin Gastroenterol Hepatol 2021;19:1502. doi:10.1016/j.cgh.2020.08.002

Jejunal venous malformations in Cowden syndrome: a case report

To the Editor,

Cowden syndrome (CS) is a rare, familial, multisystem disorder with an autosomal dominant pattern of inheritance [1], whose estimated prevalence is 1 in 200,000 to 250,000.

The clinical features of CS include macrocephaly (head circumference ≥97th percentile), Lhermitte-Duclos disease (dysplastic gangliocytoma of the cerebellum), benign mucocutaneous manifestations, and hamartomatous overgrowth in the intestinal tract [2]. Patients with Cowden Syndrome are at increased risk of malignant neoplasms in breast, thyroid, endometrium, gastrointestinal tract, and genitourinary system [2]; the pathological hallmark is the presence of a number of trichilemmomas, benign tumors originating from the outer root sheath of the hair follicle.

Cowden syndrome has been linked to germline mutations in PTEN (Phosphatase and TENsin homolog) tumor suppressor gene [2], thus causing dysfunctional cell growth. PTEN gene is expressed in vascular smooth muscle cells, where it downregulates new vessels formation through suppression of vascular endothelial growth factor (VEGF) expression. This could be a possible cause for onset of arteriovenous malformations (AVMs) in patient with CS. There are some reports describing patients with CS that had AVMs in the liver, small intestine or in the spine [3, 4]. These vascular lesions may cause acute or chronic gastrointestinal bleeding that may be difficult to diagnose [5].

A 62-year-old female patient diagnosed with CS presenting chronic anemia, was admitted to the Gastroenterology Department for endoscopic examination of the gastroenteric tract. The patient had a personal history of Addison disease, breast fibroadenolipoma, thyroidectomy for a follicular thyroid cancer, autoimmune polyserositis and vitiligo.

In 2017 she successfully underwent surgery for prophylactic total colectomy, after the endoscopic finding of multiple small polypoid colon formations and a sigma tubulovillous adenoma with moderate dysplasia grade. PTEN mutation was detected.

Physical examination revealed craniofacial abnormalities with macrocephaly and high-arched palate, multiple facial keratotic papules, scrotal tongue and diffuse cutaneous verrucous papules.

She presented a vast AVM in the shoulder-upper arm region, with functional limitation of the glenohumeral joint. Upper endoscopy revealed small raised white plaques in the esophageal mucosa (glycogenic acanthosis, pathognomonic for CD); in the stomach, multiple 3-6 mm polyps were found in antrum, as well as in duodenal bulb and second part of duodenum, with superficial erosions. The patient underwent ileoproctoscopy, showing multiple small sessile polyps (2-5 mm) in rectum.

Then, we performed single balloon enteroscopy (SIF-180, Olympus) and examined about two meters of small bowel starting from the duodenum. Intriguingly, we found many dark-blue spherical protrusions in the jejunum, covered by normal mucosa, with diameters ranging from 5 to 30 mm, which could be attributable to venous malformations (Fig. 1). Such lesions were covered with normal mucosa, therefore they were not judged to be the cause of anemia.

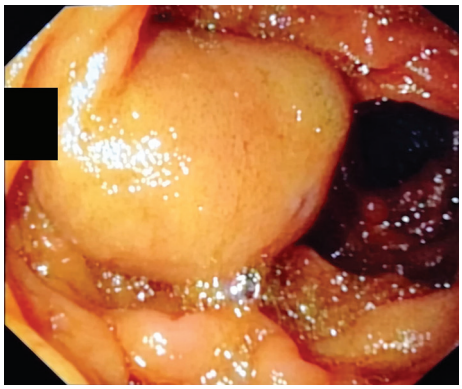

Fig. 1. Enteroscopic picture of venous malformations in the small bowel.

Venous malformations may occur in several anatomic sites in patients with CS, possibly due to impaired angiogenesis secondary to PTEN mutation. Central nervous system is the most frequently involve site for AVMs [2], while gastrointestinal malformations seem less common [3-5]. Nevertheless, our case underlines that in patients with CS and chronic anemia, investigation for other causes than gastrointestinal cancer should be carried out, and AVMs are a relevant issue to be looked for, since in some cases they may lead to massive bleeding [5]. In our case, venous malformations looked covered by normal mucosa, therefore it was unlikely that they could be the cause for anemia, while the multiple gastric eroded polyps may be a more plausible reason. For that reason, the patient underwent multiple polypectomies in a following endoscopic examination. However, presence of AVMs in a CS should be always kept in mind for prognostic reasons, in case of sudden anemia onset.

Mariapaola Piazzolla, Antonia Valeria Borraccino, Salvatore Rizzi, Giuseppe Losurdo, Alfredo Di Leo
Section of Gastroenterology, Department of Emergency and Organ Transplantation, University of Bari, Bari, Italy

Correspondence: Giuseppe Losurdo, giuseppelos@alice.it

Conflicts of interest: None.
DOI: 10.15403/jgld-4655

REFERENCES

1. Lloyd KM 2nd, Dennis M. Cowden's disease. A possible new symptom complex with multiple system involvement. Ann Intern Med 1963;58:136-142. doi:10.7326/0003-4819-58-1-136
2. Gustafson S, Zbuk KM, Scacheri C, Eng C. Cowden syndrome. Semin Oncol 2007;34:428-434. doi:10.1053/j.seminoncol.2007.07.009

3. Duhaut L, Eyries M, Lewin M, et al. Hepatic Arteriovenous Malformation: The Search for a PTEN Mutation! Hepatology 2021;74:1121-1123. doi:10.1002/hep.31694
4. Toya Y, Nakamura S, Yamaguchi S, Yanai S, Kawasaki K, Matsumoto T. Cowden syndrome with multiple venous malformations in the small bowel. Gastrointest Endosc 2016;84:747-748. doi:10.1016/j.gie.2016.01.056
5. Nakayama Y, Segawa J, Sujita K, et al. Intestinal bleeding from arteriovenous malformations of the small bowel in a patient with Cowden syndrome: report of a case. Surg Today 2013;43:542-546. doi:10.1007/s00595-012-0460-x

Fomepizole as an emerging adjunct in treating severe acetaminophen toxicity: a case report and a brief review

To the Editor,

Acetaminophen (APAP) is an important cause of acute liver failure (ALF) in the Western World. N-Acetylcysteine (NAC) is considered the primary antidote for APAP toxicity. Recent case series raised the question of adding fomepizole to existing NAC in acetaminophen poisoning, especially for patients who, despite receiving NAC are at risk for worsening liver injury [1].

A 58-year-old female with fibromyalgia and chronic alcoholism presented with confusion and recent ingestion of large amounts of extra-strength APAP for pain. The last ingestion of APAP was estimated to be 6-18 hours before admission but could not be further specified. Similarly, the amount of ingested acetaminophen was unknown, but the patient has been on acetaminophen for several days to weeks and ingested staggering doses for chronic pain. The patient denied suicidal ideation; her last alcohol consumption was reportedly multiple days ago, with no signs of alcohol withdrawal.

Initial laboratory analyses were significant for an APAP level of 126.3 ug/ml, ethanol < 0.01 gm/dl %, aspartate aminotransferase (AST) of 2,175 U/l, alanine aminotransferase (ALT) of 896 U/l, total bilirubin of 2.6 mg/dl, INR 1.6, lactate of 3.9 mmol/L and creatine kinase (CK) 151 U/L. N-Acetylcysteine rescue was immediately initiated. The 21-hour intravenous (i.v.) protocol was initially used as per state poison control recommendation. Other medications administered on admission included multivitamins and pantoprazole. A viral and autoimmune panel remained unremarkable. The imaging studies indicated patent vasculature and trace perihepatic ascites. Initially, transaminases and liver function seemed to plateau between hours 15 and 27 but eventually worsened. State poison control recommended doubling the NAC dose to 12.5 mg/kg/hour until the serum APAP level is undetectable and then continuing the NAC dose at 6.25mg/kg/hr. Acetaminophen in serum was undetectable after 40 hours.

Additionally, a one-time loading dose of 15 mg/kg i.v. fomepizole was administered, followed by four doses of 10 mg/kg every 12h. The first dose of i.v. fomepizole was given 30 hours after admission, likely consistent with 36-48 hours after the last known ingestion of acetaminophen. Irrespective of these values, the encephalopathy improved already one day after admission. King's College criteria were calculated daily but did not indicate the need for transplant evaluation. The further course of hospitalization was characterized by an acute kidney injury (AKI). Differential diagnoses included AKI in the context of APAP-induced hepatotoxicity, hepatorenal syndrome, and acute tubular necrosis. The patient was started empirically on albumin, midodrine, and octreotide. Fomepizole was continued, and the kidney function improved approximatively 80 hours post-admission with no need for hemodialysis (Supplementary file, Fig 1). The patient's liver and kidney function returned to baseline four weeks after admission.

Acetaminophen is metabolized by glucuronidation and sulfation to inactive metabolites cleared by the kidneys. Additionally, cytochrome (CYP) 2E1 complex forms N-acetyl-p-benzoquinone imine (NAPQI), which usually quickly binds to glutathione-producing nontoxic metabolites. In an APAP overdose, glutathione stores are rapidly depleted, and NAPQI results in hepatocyte necrosis and hepatic failure (Fig. 1) [2].

Our case illustrates a case of APAP-induced acute liver injury with a significant elevation in transaminases resulting in the administration of Fomepizole 36-48 hours after the last known ingestion of acetaminophen. This case was complicated by the uncertainty regarding the total amount of ingested acetaminophen. Fomepizole is more commonly known as an antidote for methanol or ethylene glycol poisoning with a known side effect profile [3]. The proposed hepatoprotective effect of fomepizole or 4-Methylpyrazole (4MP) [4] was observed in vitro studies and is related to an inhibition of CYP2E1 [5, 6], which results in a decrease of the toxic metabolite NAPQI. Additionally, 4MP prevents c-Jun N-terminal kinase (JNK) activation, an essential protein kinase involved in stress signaling pathways, including mitochondria and nuclear DNA fragmentation [7].

A product of >10,000 µg/mL* IU/L of the APAP concentration (µg/mL) and ALT or AST (IU/L), as well as worsening King's College criteria [8, 9], are valuable tools to gauge worsening liver failure despite NAC administration.

Worsening of liver function with rising transaminases resulted in the dosing of i.v. fomepizole at hour 30 of admission. Further doses were administered at hours 45, 57,69, and 81 despite APAP being undetectable in serum after 40 hours of hospitalization. The benefits of early 4MP were illustrated in vitro in human hepatocytes and in a mouse model in vivo [5]. However, recent animal data indicated that fomepizole might still be effective even when given late in the treatment [7]. Moreover, a small trial involving humans confirmed a reduced oxidative metabolism of APAP with the administration of 4MP [10].

It remains speculative what function fomepizole had in our patient regarding the underlying AKI, as a recent study indicated that fomepizole could have protective properties in preventing APAP-induced nephrotoxicity [6].

Overall, adding fomepizole to NAC in APAP poisoning remains controversial, with different opinions concerning a potential off-label use [1]. An experienced toxicologist should decide to add fomepizole to a NAC- protocol on a case-to-case basis and in agreement with the patient. Previous reported similar cases are summarised in the Supplementary file.

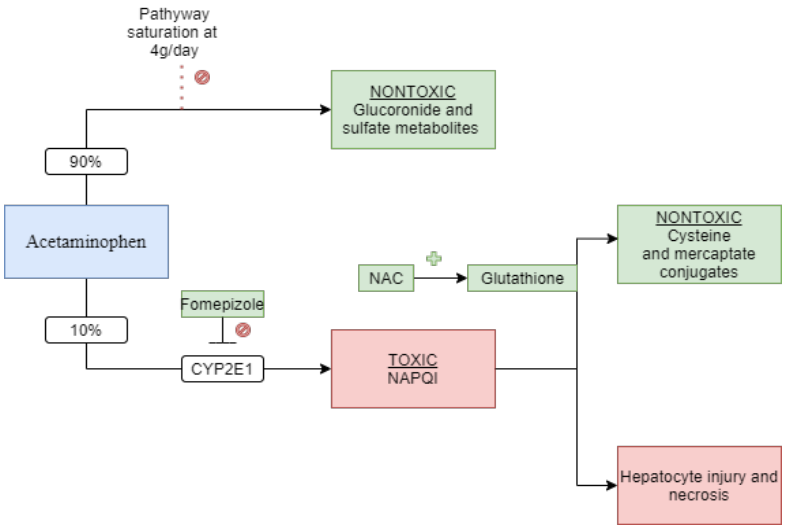

Fig. 1. Acetaminophen is primarily metabolized via glucuronidation and sulfation. When this pathway becomes oversaturated, most APAP is metabolized through CYP2E1 to toxic NAPQI. Fomepizole inhibits CYP2E1 and downstream production of NAPQI. NAC replenishes Glutathione which conjugates APAP to nontoxic cysteine and mercaptan conjugates. If glutathione is depleted, more NAPQI binds to cysteine groups causing hepatocellular necrosis [2]. NAPQI: N-acetyl-para-benzoquinoneimine.

Alexander Kusnik[1], Mostafa Reda Mostafa[1], Nicole Hunter[1], Rutwik Sharma[1], Hera Jamal[1,2], Mazin Hameed[1]
1) Department of Internal Medicine, Unity Hospital, Rochester, New York; 2) Lake Erie College of Osteopathic Medicine, USA

Correspondence: Alexander Kusnik,
alexander.kusnik@rochesterregional.org

Conflicts of interest: None.
DOI: 10.15403/jgld-4715

Supplementary material: To access the supplementary material visit the online version of the *J Gastrointestin Liver Dis* at http://dx.doi.org/10.15403/jgld-4715

REFERENCES

1. Link SL, Rampon G, Osmon S, Scalzo AJ, Rumack BH. Reply to Comments on Fomepizole as an adjunct in acetylcysteine treated acetaminophen overdose patients: a case series. Clin Toxicol (Phila) 2022;60:668-669. doi:10.1080/15563650.2021.2016799
2. Bunchorntavakul C, Reddy KR. Acetaminophen (APAP or N-Acetyl-p-Aminophenol) and Acute Liver Failure. Clin Liver Dis 2018;22:325-346. doi:10.1016/j.cld.2018.01.007
3. Bestic M, Blackford M, Reed M. Fomepizole: a critical assessment of current dosing recommendations. J Clin Pharmacol 2009;49:130-137. doi:10.1177/0091270008327142
4. Blomstrand R, Ellin A, Löf A, Ostling-Wintzell H. Biological effects and metabolic interactions after chronic and acute administration of 4-methylpyrazole and ethanol to rats. Arch Biochem Biophys 1980;199:591-605. doi:10.1016/0003-9861(80)90317-3
5. Akakpo JY, Ramachandran A, Kandel SE, et al. 4-Methylpyrazole protects against acetaminophen hepatotoxicity in mice and in primary human hepatocytes. Hum Exp Toxicol 2018;37:1310-1322. doi:10.1177/0960327118774902
6. Akakpo JY, Ramachandran A, Orhan H, Curry SC, Rumack BH, Jaeschke H. 4-methylpyrazole protects against acetaminophen-induced acute kidney injury. Toxicol Appl Pharmacol 2020;409:115317. doi:10.1016/j.taap.2020.115317
7. Akakpo JY, Ramachandran A, Duan L, et al. Delayed Treatment With 4-Methylpyrazole Protects Against Acetaminophen Hepatotoxicity in Mice by Inhibition of c-Jun n-Terminal Kinase. Toxicol Sci 2019;170:57-68. doi:10.1093/toxsci/kfz077
8. Wong A, Sivilotti ML, Dargan PI, Wood DM, Greene SL. External validation of the paracetamol-aminotransferase multiplication product to predict hepatotoxicity from paracetamol overdose. Clin Toxicol (Phila) 2015;53:807-814. doi:10.3109/15563650.2015.1066507
9. McPhail MJ, Farne H, Senvar N, Wendon JA, Bernal W. Ability of King's College Criteria and Model for End-Stage Liver Disease Scores to Predict Mortality of Patients With Acute Liver Failure: A Meta-analysis. Clin Gastroenterol Hepatol 2016;14:516-525.e5. doi:10.1016/j.cgh.2015.10.007
10. Kang AM, Padilla-Jones A, Fisher ES, et al. The Effect of 4-Methylpyrazole on Oxidative Metabolism of Acetaminophen in Human Volunteers. J Med Toxicol 2020;16:169-176. doi:10.1007/s13181-019-00740-z