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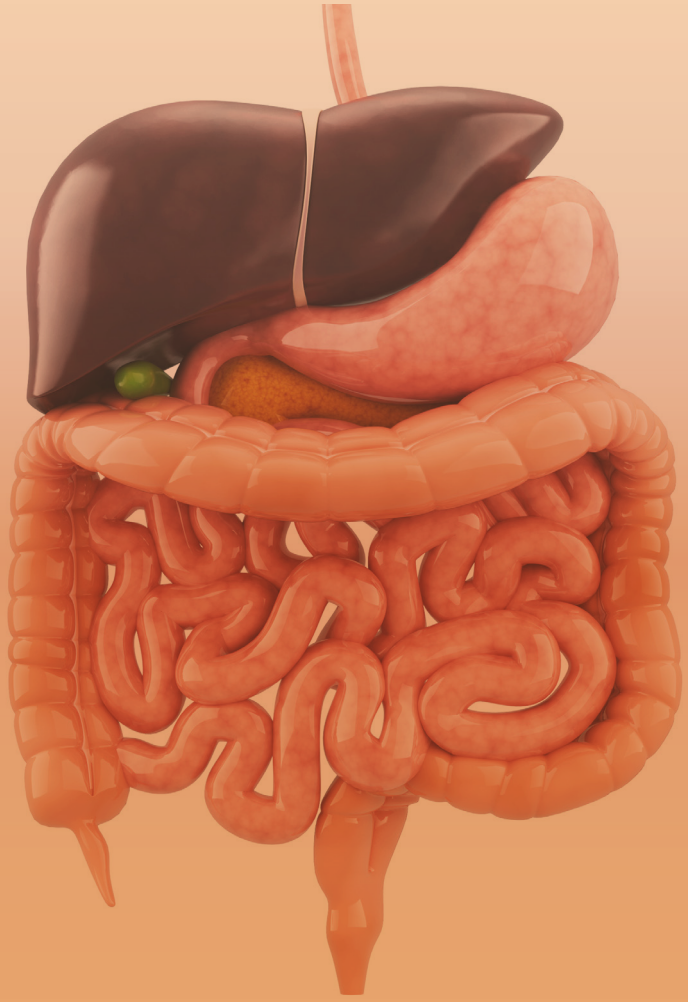

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Case Report

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Coalescent Cyclical Vomiting: A Manifestation of Narcotic Bowel Syndrome?

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ABSTRACT

This illustrative case suggests mechanisms that may contribute to disease progression and complications in adults with Cyclical Vomiting Syndrome (CVS). Symptoms initially followed a characteristic pattern in the context of marijuana use and led to repeated hospitalizations. Escalating opioid use for pain control resulted in coalescence of the syndrome with more frequent and severe emetic episodes, ultimately complicated by an esophageal microperforation. While analgesic therapy may play an important role in management of acute exacerbations, ongoing use of narcotics may contribute to the development of refractory CVS. This association of disease progression with opiates suggests that coalescent CVS should be considered a foregut manifestation of narcotic bowel syndrome.

KEYWORDS: Cyclical vomiting syndrome; Coalescing attack; Opioids; Narcotic bowel syndrome.

CASE REPORT

A 35 year-old man presented with an acute exacerbation of chronic abdominal pain, Nausea and Vomiting (N&V). The pain was severe, unrelenting and affected the entire abdomen with an epicenter in the Left Lower Quadrant (LLQ). He also experienced vomiting every 15-20 minutes. After several episodes of emesis, he had noticed sharp and then continuing pain in the center of the chest.

He had a long history of sudden episodes of abdominal pain, starting at the age of twenty. Initially, he had suffered from a sudden onset of pain associated with nausea and vomiting with a frequency of more than 20 times per day. Typically, such episodes woke him up in the early morning hours, persisted for several hours and eventually led to dehydration, requiring emergency room visits and even repeated hospitalizations. He could often alleviate milder symptoms by taking hot showers or baths. Emetic episodes lasted for up to one week and were followed by prolonged asymptomatic periods. However, his symptoms gradually progressed. Eventually, he received chronic opioid therapy for the recurrent pain, which was associated with an even more significant rise in the frequency of exacerbations. He had previously been diagnosed as suffering from irritable bowel syndrome, anxiety and depression. During the 6 years prior to his current presentation, he had undergone more than 20 abdominal computerized tomographies and ten upper endoscopies, which had all shown varying degrees of esophagitis or occasional Mallory Weiss tears. Additional diagnostic studies had excluded pancreatic disease, hereditary angioedema, porphyria, gastroparesis, and small bowel or colonic disease.

His outpatient medications included buprenorphine and naloxone, hydromorphone as needed, dicyclomine, gabapentin and citalopram. He regularly smoked marijuana since his teenage years. His family history was negative for migraines or CVS.

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On admission, he complained about severe pain, was normotensive, but tachycardic. The key physical examination findings were a dry oral mucosa, subcutaneous crepitus in neck and anterior chest and diffuse abdominal tenderness without guarding or rebound. He had evidence of dehydration with hemoglobin of 18 g/dl, hematocrit 54.1%, and a creatinine of 4.2 mg/dl with associated anion ion gap acidosis. Imaging studies demonstrated a pneumomediastinum (Figure 1) with subcutaneous emphysema. As an esophagram did not show a contrast leak, he was treated conservatively with intravenous fluids, antiemetics, analgesic agents, acid suppression and antibiotics. He recovered and was discharged with the diagnosis of coalescent CVS, complicated by an esophageal microperforation. His treatment goal was to taper and then completely discontinue opioids and to stop cannabinoid use. To blunt the expected autonomic response associated with withdrawal, he received clonidine and was switched from citalopram to a Tricyclic antidepressant (TCA).

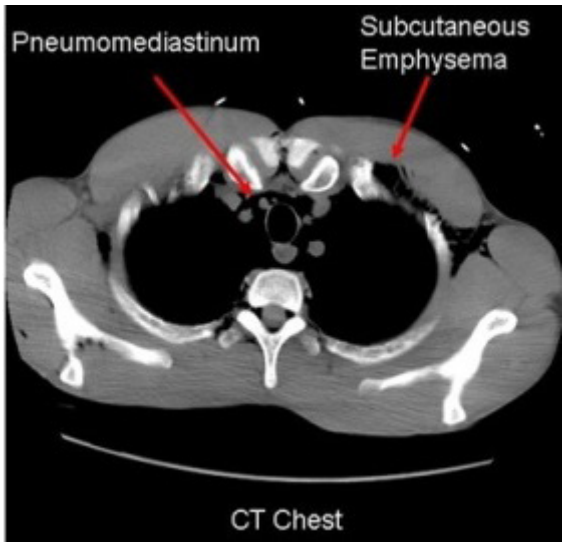

Figure 1: Pneumomediastinum with subcutaneous emphysema.

DISCUSSION

This case highlights several key points that are important for patients and physicians who deal with CVS, an unexplained disorder first described in children but now increasingly recognized in adults. The patient's esophageal perforation was a secondary complication of repetitive vomiting, which more commonly causes esophagitis or gastrointestinal bleeding due to Mallory Weiss tears. Even though the apparent microperforation of the esophagus is an extreme example, it still emphasizes the need to identify an underlying disorder rather than focusing exclusively on the important consequences of repetitive vomiting. While only seen in a subset of patients, the case also illustrates the fact that CVS can undergo a phenotypic switch from its classic, dichotomous patterns of emetic and asymptomatic phases to eventual coalescence of increasingly frequent attacks with chronic nausea and pain complicated by typical exacerbations.[1,2] Only a detailed history revealed that the patient clearly met diagnostic criteria for CVS (Table 1) at the onset of his illness. The progression of his illness was associated with the introduction of chronic opioid use to control symptoms, a change that has been linked the development of refractory disease.[3]

Adults – Rome III Criteria[11]	Children – *NASPGHAN Guidelines[12]
Must include all of the following: 1. Stereotypical episodes of vomiting with a) Acute onset b) Duration <1 week 2. Three or more discrete episodes in the prior year. 3. Asymptomatic intervals between emetic phases. Supportive criterion: Personal or family history of migraine headaches.	1. At least 5 attack in any interval, or a minimum of 3 attacks during a 6 month period. 2. Episodic attacks of intense nausea and vomiting lasting 1 h-10 days and occurring at least 1 week apart. 3. Stereotypical pattern and symptoms in the individual patient. 4. Vomiting during attacks occurs at least 4 times/hour 5. Asymptomatic intervals between emetic phases. Absence of other specific causes.

*NASPGHAN: North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition

Table 1: Criteria for CVS in adults and children.

Diagnosing CVS remains a challenge, and many patients undergo repeated and typically negative diagnostic evaluations, or even surgical treatments, before the diagnosis is entertained. Tests do not only constitute a financial burden, but also come with a risk, for example due to cumulative radiation exposure with radiographic testing or the risk of repeated endoscopic evaluations. The patient's history also supports the need to recognize the strong association of cannabinoid use with the development of CVS, as cannabis use has been found to contribute to the development of CVS in about 50% of the patients.[4-7]

Acutely, the patient improved with symptom-driven management strategy that largely relied on intravenous analgesics, antiemetics and fluids.[8] However, long-term treatment of CVS with preventative strategies is essential to reduce the number of attacks. After recognizing the disease, physicians need to identify potential triggers, such as opioid and cannabinoid use, both of which contributed in the case described. With the emergence of dependence, discontinuation of opioids or cannabinoids will trigger withdrawal symptoms that mirror emetic episodes of CVS. Thus, a slower taper may be required to prevent withdrawal in these individuals. In addition, clonidine and TCAs should be considered to blunt to autonomic response associated with withdrawal.[9] TCAs remain the treatment of choice as preventative therapy for patients with CVS.[2] Should TCAs fail or be contraindicated, coenzyme Q10 or anticonvulsive drugs may be acceptable alternatives.[10-12] Seen in a broader context, our observation suggests that coalescing CVS is a foregut manifestation of the narcotic bowel syndrome and will require a multidisciplinary approach to achieve long-term remission.

CONFLICTS OF INTEREST

Authors have no conflicts of interest or financial disclosure to make.

CONSENT

No consent is required to our article publication.

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Research

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Management of Inflammatory Bowel Diseases in Jehovah's Witness

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ABSTRACT

Background: Treatment of Inflammatory Bowel Disease (IBD) patients who are known to be Jehovah's Witness (JW) can be a unique challenge. JW accept most available medical treatments, but may not accept blood transfusions or blood products due to their religious beliefs. We looked at the experience of treating IBD in JW, their care during acute bleed and also the outcome.

Methods: A retrospective review was performed to identify patients treated for IBD known to be JW between the years 2005-2009 at two University of Pittsburgh Medical Center Hospitals. Demographic data, clinical presentation, treatment during hospitalizations and outpatient clinics were abstracted from the chart. All patients were confirmed to be having IBD either by colonoscopy or by documented evidence during clinical care. JW was confirmed by documentation in the chart. We took note of complications secondary to IBD, treatment measures during emergent conditions like acute bleed, bowel obstruction and also different treatment options used for long term management of IBD.

Results: Twenty two patients were identified in both the university (n=14) and community hospital (n=8). Out of them, 13 patients had ulcerative colitis and 9 had Crohn's disease. Caucasians comprised majority of the population (68%). Mean age was 51 years. Mean time interval between initial diagnosis and most recent follow-up was 14 years. Among study subjects, 68% had documented colonoscopy reports with 6 patients (27%) showing active disease. Nine (41%) of these patients were post surgical and 6(27%) patients developed complication (clostridium difficile, abscess, fistula, colon cancer and small bowel obstruction) secondary to their IBD. Seventeen (77%) IBD patients were treated as an outpatient and 5(23%) as an inpatient. Three (14%) patients had to be admitted to Intensive Care Unit (ICU) during their inpatient stay. Hemoglobin was more than 10 g/dl in 68%, between 7 to 10 g/dl in 18% and less than 7 g/dl in 14% at baseline. After treatment with conservative measures for anemia, hemoglobin improved to more than 10 g/dl in 91%, and between 7 to 10 g/dl in 9%. One patient died with organ failure secondary to sepsis. Two patients (9%) underwent bloodless surgery with cell saver technique with no mortality.

Conclusion: Management of IBD related anemia in JW has a good outcome and can be treated conservatively without blood transfusion. Complications secondary to IBD does not adversely affect the outcome.

KEYWORDS: Inflammatory bowel disease; Jehovah's Witness; Blood transfusion; Bowel obstruction.

ABBREVIATIONS: IBD: Inflammatory Bowel Disease; JW: Jehovah's Witness; ICU: Intensive Care Unit; UPMC: University of Pittsburgh Medical Center; IRB: Institutional Review Board; UH: University Hospital; CH: Community Hospital.

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BACKGROUND

Medicine is not only providing health care to the society, but it also incorporates respecting religious beliefs of individual members of the society and providing the best care possible with the available resources. Jehovah's Witnesses (JW) are distinct from other members of community where medical management dissects with their religious beliefs. JW are actively present in many countries but do not form the major religious group in any country. As per the 2013 yearbook of JW, worldwide population of JW who are actively involved is roughly 7.7 million.[1] Their estimated world-wide growth rate is around 2.1% with 3.8 million individuals in the US following this practice. There is a common belief among this group of individuals to not use blood transfusions or blood derived products due to religious beliefs. JW consider whole blood transfusion as a violation of God's law. Main body of JW directs followers to refuse blood transfusions in a "*life-or-death situation*" and many times acceptance of blood transfusion may lead to their expulsion from the religion and life-long social suffering.

However, when such individuals presents for medical issues where such drastic measures are necessary, it becomes an ethical dilemma for the care provider. One of such area is Inflammatory Bowel Disease (IBD) in JW. Lakatos, et al. reports incidence rate of ulcerative colitis can be up to 24.5/100,000 persons, while that of crohn's disease can be up to 16/100,000 persons worldwide, with the prevalence rate of IBD up to 396/100,000 persons.[2] CDC quotes that estimated people suffering from IBD is up to 1.4 million in the United States. Incidence and prevalence of this debilitating disease is increasing as per current systematic review conducted by Molodecky, et al. which reports highest prevalence rate of UC around 249 per 100,000 persons and that of CD to be around 319 per 100,000 persons in North America.[3] Exact incidence and prevalence of IBD in JW is not available in literature as per our knowledge, however, we can extrapolate these results to JW as there is no lower incidence or immunity to IBD has been reported earlier in them.

Proper management of IBD patients who are known to be JW can be a unique challenge as they accept most available medical treatments, but not blood transfusions or blood products. In this situation, ethical dilemma arises when there is a need for blood products in life-or-death scenario due to severe gastrointestinal bleeding, those who undergoes surgery and had major blood loss and acute anemia. There are no prior studies regarding management of IBD in JW, common problems encountered, interventions to avoid acute complications, long-term outcomes compared to general population and if there is any disparity in these outcomes compared to general population affected with IBD. We looked at the experience of treating IBD in JW, their care during acute bleed and also the outcome at two major hospitals of University of Pittsburgh Medical Center (UPMC). Aim of the present study was to initiate understanding of management of IBD in JW in order to improve their long-term outcomes in IBD patients.

METHODS AND PATIENTS

This was a retrospective study conducted during year 2010 at two hospitals of University of Pittsburgh Medical Center (UPMC). A retrospective review was performed to identify patients treated for IBD known to be JW between the years 2005 to 2009 at these two locations. We obtained Institutional Review Board approval (IRB) from individual hospitals of UPMC where study was carried out including University Hospital (UH) and Community Hospital (CH). Retrospective analysis identified total of 22 patients with known tissue diagnosis of IBD and were active JW. (University [UH], n=14 and community [CH], n=8). All patients were confirmed to be having IBD either by colonoscopy or by documented evidence during clinical care. Individuals were approached for informed consent for data pertaining to their care only and no other identifiable information. Their demographic data including age, gender, ethnicity, clinical presentation, treatment during hospitalizations and outpatient were abstracted from the chart. We also took note of complications (clostridium difficile, abscess, fistula, colonic cancer and small bowel obstruction) secondary to IBD in the hospital or as an outpatient. Treatment measures during emergent conditions like acute bleed, bowel obstruction and also different treatment options used for long term management of IBD were also noted. All the data were secured and analyzed by statistical software and use of Microsoft Office 2010. Patient characteristics and demographic variables were calculated by their means and percentage distribution among subjects. Similarly, frequency distributions of other variables were drawn: medications, complications, treatment of anemia and others.[4]

RESULTS

Patient characteristics are shown in Table 1. Among total of twenty-two patients who were JW and also had active or stable IBD including Crohn's disease or ulcerative colitis, males and females were equally distributed. Majority of them were Caucasians (68%) followed by African Americans (32%). Mean age of the patients was 51 years. Ulcerative colitis was diagnosed in 59% of individuals while remaining 41% had Crohn's disease. Among all the subjects, 77% were being managed as an outpatient while 23% were hospitalized for either flare of the disease, complication or other problems unrelated to IBD. Mean time interval between initial diagnosis and most recent follow up was 14 years. 68% of the subjects had documented colonoscopy reports with 27% showing active disease. Twenty-seven percent of the study patients had at least one of the following complications: clostridium difficile infection, abscess, fistula, colon cancer due to IBD and small bowel obstruction. Approximately 41% of them underwent surgery for complications. Half of the patients were on 5-ASA [Amino Salicylic Acid] agents (mesalamine, sulfasalazine or other 5-ASA), 18% of the patients were on immunomodulators including azathioprine, and 9% were on biologics including infliximab.

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Total number of patients	22
Age, mean	51 years
Gender Male Female	 11 11
Ethnicity Caucasians African Americans	 15(68%) 7(32%)
Median follow up	14 years
Ulcerative Colitis	13(59%)
Crohn's disease	9(41%)
Active disease	6(27%)
Post surgical	9(41%)
Complications	6(27%)
Outpatient management	17(77%)
Inpatient management	5(23%)
Intensive care unit	3(14%)
Medications 5 ASA Immune modulators Biologics	 11(50%) 4(18%) 2(9%)
Bloodless surgery	2(9%)
Death due to sepsis	1(5%)

Table 1: Patient characteristics N(%).

Blood tests revealed hemoglobin >10 g/dl in 68%, between 7 to 10 g/dl in 18% and <7 g/dl in 14%. After treatment for anemia, hemoglobin increased to more than 10 g/dl in 91%, and to 7 to 10 g/dl in 9% of the individuals. Table 2 represents different forms of treatments employed to treat symptomatic anemia. Oral (89%) or intravenous (11%) iron was the major form of treatment for chronic blood loss anemia (41%), followed by vitamin supplementation (32%). Red blood cell colony-stimulating factors erythropoietin was used in 18% of patients. Other agents which were used in the event of bleeding were: vitamin K (9%), albumin (5%) and desmopression (5%).

Iron (oral-89%, Intravenous-11%)	9(41%)
Vitamin B12	1(5%)
Folic acid	6(27%)
Erythropoietin	4(18%)
Vitamin K	2(9%)
Albumin	1(5%)
Desmopressin	1(5%)

Table 2: Treatment of anemia N(%).

Approximately, 14% patients were admitted to intensive care unit (ICU) due to some form of complication requiring ICU admission. One of patients received albumin, desmopressin, ionotropes and blood transfusion with consent for stabilization in ICU. Unfortunately, this patient died with organ failure secondary to sepsis. Rest of the patients who were admitted to ICU (9%), underwent bloodless surgery with cell saver technique with no mortality.

DISCUSSION

Our study is the first study in this population on IBD and objective was to start understanding whether any disparities exist on the basis of our prior understanding of IBD and its management. Although the study was performed on a small scale, following conclusions can be drawn. Results infer that treating IBD patients in JW carries good outcomes especially considering anemia treatment with conventional standards. Majority of patients can be treated in outpatient setting. Vigilant outpatient monitoring of blood counts as well as hemoglobin and pre-emptive iron and vitamin replacement can be useful in this individuals. Early recognition of anemia due to underlying IBD is essential for this population as they might refuse BT when it is severe requiring blood transfusion. In limitation of prior evidence in place in this vulnerable population, this study provides preliminary data regarding need for further introspection in this subject.

Most of the physicians in the setting of Gastrointestinal (GI) bleeding in IBD in JW are not comfortable due to the prior conception of JW's refusal of blood products. This might create assumption of difficulty in treating this population. While our data suggests that GI bleeding in IBD can be managed without giving them blood and by using alternate measures. In fact, few of the patients were critically ill in this study and underwent surgery however they still managed to do well with no deaths related to anemia or acute blood loss. In fact, a restrictive transfusion strategy as demonstrated by current evidence supports this fact indirectly.[5] Our study albeit with a small sample size indicates that conservative management in this population is no different than other religious groups. Complications of IBD in JW can be managed similarly as in general population with IBD.

Chronic anemia occurs in approximately 1/3 of patients with IBD and half of the IBD patients are iron-deficient.[6] Importance of using Intravenous (IV) iron replacement early on has been well-established. This approach avoids allogeneic blood transfusions and improves quality of life in IBD patients.[7,8] IV iron is safe and effective in the treatment of iron deficiency anemia in IBD patients, and erythropoietin is useful in a subset of patients with refractory anemia.[9] Recently, Litton, et al. reported findings of systematic review and meta-analysis of randomized controlled trials investigating the safety and efficacy of intravenous iron therapy in reducing requirement of allogeneic red blood cell transfusions.[10] Authors conclude that intravenous iron therapy is effective in increasing hemoglobin concentration, especially when erythroid stimulating agents are used and reducing the risk of allogeneic Red Blood Cell (RBC) transfusion and could have broad applicability to a range of acute care settings. Ball, et al. reported successful use of recombinant human erythropoietin in critically ill JW to stimulate red blood cells and prevent severe life-threatening anemia after review of prior case reports.[11] Sparling, et al. used erythropoietin preoperatively in the management of JW who were about to have revision total hip arthroplasty and reported their utility in achieving higher hematocrit pre-operatively because of their elective nature and the

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moderately flexible timing associated with these procedures.[12] In this study, majority of patients were closely monitored easily as an outpatient with management of their blood loss anemia with iron supplementation as well as vitamin supplementation with improvement in their hemoglobin. This is the pattern commonly seen in general population with IBD. Those who were admitted in hospital also did well and only one patient actually required blood transfusion. With the advent of bloodless surgery, ethical dilemma of transfusion will get further narrower. Most presume that mortality is high without supportive blood. This is a good study to show that it is not the case and they can be managed well with no mortality and that outcomes are good. Thus, conservative anemia management with iron and if necessary, erythropoietin, in IBD patients who are JW can prevent their requirement for allogeneic blood transfusions.

Last decade has seen many advances in care of JW especially regarding alternatives for blood transfusions. Majeski, et al, reported surgical case series of 132 JW patients.[13] Following alternatives were suggested instead of transfusion of blood such as erythropoietin, iron dextran, aprotinin and Fluosol-DA 20%. Majeski, et al. further reported that technological surgical developments and advances, like the cell saver technique, argon beam coagulator, acute limited normovolemichemodilution, autologous whole plasma fibrin gel, and controlled hypotensive anesthesia during anesthesia have contributed substantially to a reduction in the operative loss of blood. Recent reviews also report uses of these alternative strategies and that despite their belief regarding transfusion, JW do not have a higher mortality rate after traumatic injury or surgery, especially if hemoglobin is kept at least 7 g/dL.[14]

Previous literature mentioned that iron replacement or other conservative treatment like erythropoietin use lead to improved hemoglobin and later the surgery was undertaken. This was done instead of using blood transfusion when individual with JW refused them before proceeding with surgery. Obviously, similar rules cannot be applied in emergent life-saving surgeries. Autologous blood transfusion or cell-saver technique can be offered in later scenario. With the cell saver technique, those individuals who has to undergo surgery can be transfused their own blood. In last decade, bloodless surgery and bloodless management program have been studied thoroughly and guidelines have been suggested.[15-17] It is being practiced at many centers nowadays. It will benefit not only individuals who are JW, but also individuals were refuse blood transfusion or not candidates due to earlier complication or possible risk.

Current study provides baseline information on treatment of anemia in JW and future studies with larger sample size should be carried out to study these findings. Many JW, who decline blood transfusions on religious beliefs, have been able to undergo complex medical and surgical procedures with conservative measures including iron replacement, erythropoietin and other pharmacologic measures. Our study stands in agreement with this fact as a first study among IBD patients. With growing JW population and requirement of surgery, this will be a big health care issue. Blood-free major surgery is a technological challenge in JW. Milligan, et al. mentions that techniques learnt from treating them may prove beneficial to all patients undergoing major surgery.[18] Although JW do not accept allogeneic blood transfusion, it is desirable to avoid blood transfusion in any surgical patients and application of blood conservative strategies might help reduce blood loss in any patient.[16] This is important not only from the aspect of taking care of JW, but also in general to reduce complications associated with blood transfusions - infection, volume overload, and blood transfusion associated reactions. We expect that with the advent of bloodless medicine, JW will benefit in future as well as general population. We recommend further studying IBD in JW to understand better strategies to manage IBD as well as blood loss anemia with a larger sample size. Increasing prevalence of IBD also makes requirement for blood products and health care expenditure a concern, therefore, it is essential to find ways to prevent complications due to IBD requiring surgery as well as finding techniques to minimize blood loss.

CONCLUSION

JW suffering from IBD does not endorse any disparity compared to general population and can be managed in similar fashion to the general population. Use of blood transfusion or blood products to treat anemia due to IBD in JW can be perplexing however manageable with other conservative modalities and results are similar as in general population. Most presume that mortality is high without supportive blood. This is a good study to show that it is not the case and they can be managed well with no mortality and that outcomes are good.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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Review

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Role of Calcium in Vomiting: Revelations from the Least Shrew Model of Emesis

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ABSTRACT

Cisplatin-like chemotherapeutics cause vomiting *via* release of multiple neurotransmitters (dopamine, serotonin, or substance P) from the gastrointestinal enterochromaffin cells and/or the brainstem *via* a Calcium (Ca^{2+}) dependent process. In addition, evidence from literature indicate that Ca^{2+} signaling is also triggered subsequent to activation of other emetogenic receptors including serotonergic 5-HT_3, tachykinin NK_1, dopamine D_2, and histaminergic H_1 receptors. Moreover, other emetogens such as prostaglandins, cisplatin, rotavirus NSP4 protein and bacterial toxins have the ability to induce intracellular Ca^{2+} elevation. Our findings demonstrate that application of the L-type Ca^{2+} channel (LTCC) agonist FPL-64176 or the Ca^{2+} mobilizing agent thapsigargin (a sarco/endoplasmic reticulum Ca^{2+}-ATPase inhibitor) cause vomiting in the least shrew, whereas blockade of LTCC by corresponding antagonists (nifedipine or amlodipine) not only provide broad-spectrum antiemetic activity against diverse emetogens including agonists of 5-HT_3 (e.g. 5-HT or 2-Me-5-HT)-, NK_1(GR73632)-, D_2 (apomorphine or quinpirole)-, and M_1 (McN-A343)-receptors, but can also potentiate the antiemetic efficacy of well-established antiemetic palonosetron against the non-specific emetogen, cisplatin. The transmission of emesis signals in the gastrointestinal tract and brainstem is crucially dependent on Ca^{2+} channels in neurons. In this review, we will examine the current knowledge on the role of Ca^{2+} channels and Ca^{2+}-dependent signaling pathways in the perception and modulation of emesis.

KEYWORDS: Calcium; Cisplatin; 5-HT_3 receptor; L-type Ca^{2+} channel; Ryanodine receptor; Signaling pathway.

ABBREVIATIONS: LTCC: L-type Ca^{2+} channel; GIT: Gastrointestinaltract; DVC: Dorsal Vagal Complex; DMNX: Dorsal Motor Nucleus of the Vagus; AP: Area Postrema; NTS: Nucleus Tractus Solitarius; ER: Endoplasmic Reticulum; VOCs: Voltage-Operated Channels; ROCs: Receptor-Operated Channels; SMOCs: Second Messenger-Operated Channels; SOCs: Store-Operated Channels; EC: Enterochromaffin; SERCA: Sarcoplasmic/Endoplasmic Reticulum Ca^{2+}-ATPase; SER: Sarcoplasmic/Endoplasmic Reticulum; IP_3Rs: Inositol Trisphosphate Receptors; RyRs: Ryanodine Receptors; TRPC: Transient Receptor Potential Channels; SOCE: Store-Operated Ca^{2+} Entry; CRAC: Ca^{2+} Release-Activated Channels; TRPC: Transient Receptor Potential Channels; STIM1: Stromal interacting molecule 1; CICR: Calcium-Induced Calcium-Release; PKA: Protein Kinase A.

CALCIUM HYPOTHESIS OF EMESIS

Many neurotransmitters/drugs have been implicated in the induction of vomiting including dopamine, acetylcholine, histamine, opiates, serotonin (5-HT), substance P (SP), prostaglandins and leukotrienes, to name a few.[1] Chemotherapeutics such as cisplatin induce vomiting *via* the release of a number of the above-discussed neurotransmitters/mediators in both the Gastrointestinal tract (GIT) and the brainstem Dorsal Vagal Complex (DVC) emetic nuclei including the Nucleus Tractus Solitarius (NTS), the Dorsal Motor Nucleus of the Vagus (DMNX) and the Area Postrema (AP).[1] Calcium (Ca^{2+}) is one of the simplest yet most dynamic signaling ions poised at the center of a complex network of signal transduction pathways whose

integration controls cellular pathophysiology. At rest, diverse cells have strict and well-regulated mechanisms to maintain low nM cytosolic Ca^{2+} levels.[2] However, in response to synaptic activity, cytosolic Ca^{2+} can be elevated up to 5 µM. Thus, agonists can increase cytosolic Ca^{2+} levels *via* both mobilization of intracellular stores (e.g. Endoplasmic Reticulum=ER) and influx from extracellular fluid.[3] The NK_1 receptor is G-protein coupled and can increase cytoplasmic Ca^{2+} concentration *via* extracellular influx.[3-5] In addition, the 5-HT_3 receptor is a Ca^{2+}-permeable ligand-gated ion channel.[6] 5-HT_3 receptor can evoke membrane depolarization which consequently increases cytoplasmic Ca^{2+} levels *via* extracellular influx through L-type- and 5-HT_3-receptor Ca^{2+}-permeable channels.[6-9] Other emetogens such as agonists of dopamine D_2,[10,11] cholinergic M_1,[12,13] histaminergic H_1[14,15] and opiate u[16,17]-receptors, as well as cisplatin,[18] prostaglandins,[19,20] rotavirus NSP4 protein[21,22] and bacterial toxins[23,24] have also the potential to induce extracellular Ca^{2+} influx. Therefore Ca^{2+} mobilization can be an important aspect of emesis induction since it is involved in triggering neurotransmitter release, coupled with receptor activation and excitation-transcription coupling.[25]

L-TYPE CA^{2+} CHANNELS AND EMESIS

Emetic Potential of L-type Ca^{2+} Channel Agonists

A variety of Ca^{2+}-permeable ion-channels are present in the plasma membrane, which allow extracellular Ca^{2+} influx into the cell. These include Voltage-Operated Channels (VOCs), Receptor-Operated Channels (ROCs), Second Messenger-Operated Channels (SMOCs) and Store-Operated Channels (SOCs). Voltage-gated Ca^{2+} channels can be divided into L-type, P/Q-type, N-type, R-type, and T-type.[25] Voltage-gated L-type Ca^{2+} channels (LTCCs) are activated by membrane depolarization, and serve as the principal route of Ca^{2+} entry in electrically excitable cells such as neurons and muscle.[26,27] Our study[28] provided the first evidence that the opening of plasma membrane LTCCs by the corresponding selective agonist FPL-64176[29] produces robust vomiting both in terms of its frequency and the percentage of animals vomiting. All tested shrews vomited at the 10 mg/kg dose of FPL 64176 administered intraperitoneally (i.p.).

Antiemetic Potential of LTCC Blockers

Nifedipine along with amlodipine, are among the most studied of Ca^{2+} channels blockers, and both belong to the dihydropyridine subgroup of LTCC antagonists. Relative to nifedipine, a short-acting LTCC antagonist; amlodipine is much longer acting, with a larger volume of distribution and more gradual elimination.[30-32] We have evaluated the broad-spectrum antiemetic potential of nifedipine[28] and amlodipine[33] against diverse specific (e.g. receptor selective or non-selective agonists) and non-specific (e.g. cisplatin) emetogens. Both nifedipine and amlodipine exhibited broad-spectrum antiemetic activity against diverse emetogens, however, their potency and efficacy differed substantially (Table 1). More specifically, amlodipine pretreatment significantly attenuated both the frequency and percentage of shrews vomiting in response to:

i. FPL-64176 (10 mg/kg, i.p.) in a dose-dependent manner, and provided complete protection at 5-10 mg/kg. In comparison, nifedipine reduced these emetic parameters with ID_{50} values 3.5 to 6.4 times lower. Precisely, pretreatment with nifedipine significantly attenuated the frequency and percentage of FPL-64176-induced vomiting in a dose-dependent manner with significant reductions occurring at its 0.5, 2.5 and 5 mg/kg doses. Thus, FPL-64176-induced emesis appears to be more sensitive to nifedipine.

ii. The peripherally-acting and non-selective 5-HT_3 receptor agonist 5-HT (5 mg/kg, i.p.) with substantial protection at 5 and complete protection at 10 mg/kg. Likewise, nifedipine pretreatment (1 and 2.5 mg/kg) blocked emesis caused by 5-HT in a dose-dependent but more potent manner with significant suppression in both the frequency and percentage of shrews vomiting at its 2.5 mg/kg. In addition, amlodipine in a dose-profile similar to that of nifedipine, suppressed both the frequency and percentage of shrews vomiting caused by the peripherally/centrally-acting and more selective 5-HT_3R agonist 2-Me-5-HT (5 mg/kg, i.p.) with respective ID_{50} values 2-12 times larger than that of nifedipine.[28,33] Thus, comparatively nifedipine appears to be more potent than amlodipine in suppression of emetic behaviors evoked by 2-Me-5-HT.

iii. The dopamine D_2 receptor-preferring agonist quinpirole (2 mg/kg, i.p.). However, amlodipine only managed to significantly suppress the frequency of the induced vomiting by 80-90% in 40-50% of tested shrews with respective ID_{50} values 20-24 times larger than that of nifedipine. Moreover, while nifedipine totally protected shrews from quinpirole (2 mg/kg)-induced emesis at 1 mg/kg, amlodipine had no such effect even at larger doses. Unexpectedly, both antiemetics, in a similar dose-range, suppressed both the frequency and percentage of shrews vomiting in response to the non-selective dopamine D_2receptor agonist apomorphine (2 mg/kg, i.p.) with identical ID_{50} values (Table 1).

iv. The non-selective cholinergic agonist pilocarpine (2 mg/kg, i.p.) with respective ID_{50} values between 2 and 4.6 mg/kg, whereas nifedipine lacked such efficacy. On the contrary, both amlodipine and nifedipine dose-dependently suppressed the described emetic parameters in response to administration of the M_1-preferring cholinergic agonist, McN-A343 (2 mg/kg, i.p.), nifedipine being 5 times more potent with complete vomit protection achieved at the 5 mg/kg dose (Table 1).

v. The selective tachykinin NK_1 receptor agonist GR73632 (5 mg/kg, i.p.). However, the vomit frequency was reduced by 90% at the 10 mg/kg dose of amlodipine, and complete protection was only afforded in 50% of shrews at this dose. Nifedipine not only appears to be 7-12 times more potent than amlodipine in reducing the GR73632-induced emetic parameters by 50%, but also provides complete protection at 5 mg/kg.

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Emetogens	Amlodipine ID_{50}(mg/kg)		Nifedipine ID_{50}(mg/kg)	
	Frequency	Percent inhibition	Frequency	Percent inhibition
FPL 64176	1.10(0.43-2.80)	2.70(1.40- 5.30)	0.31(0.15-0.62)	0.42(0.19-0.90)
5-HT	2.00(0.80-5.20)	3.20(1.60-6.50)	0.22(0.03-1.50)	0.91(0.42-1.90)
2-Me-5-HT	0.65(0.30-1.40)	3.10(1.40-6.60)	0.053(0.02-0.17)	1.34(0.64-2.80)
Apomorphine	0.90(0.30-2.60)	2 .00(0.94-4.30)	0.91(0.32-2.60)	2.02(0.90-4.40)
Quinpirole	2.00(0.78-5.30)	4.40(1.90-10.0)	0.10(0.03-0.36)	0.18(0.09-0.38)
Pilocarpine	2.10(0.69-6.20)	4.60(2.20-9.40)	nd	nd
McN-A-343	2.30(0.61-8.50)	3.20(1.50-7.10)	0.38(0.06-2.30)	0.95(0.43-2.10)
GR73632	1.37(0.62-3.00)	7.10(3.40-14.6)	0.19(0.08-0.43)	0.60(0.28-1.30)

*Obtained from Darmani et al 2014 and Zhong et al., 2014a.[28,33]
nd=not determined.

Table 1: Respective antiemetic ID_{50} values for amlodipine and *nifedipine against vomiting caused by diverse emetogens.

Thus, nifedipine appears to be 2-24 times more potent than amlodipine against vomiting caused by FPL 64176, 5-HT, 2-Me-5-HT, GR73632, quinpirole and McN-A343. These potency disparities could be explained in terms of their pharmacokinetic and pharmacodynamic differences. In fact nifedipine has a rapid onset of action and reaches peak plasma concentration within 30 min of administration with a short duration of action (half-life=1-2 h).[34,35] On the other hand, amlodipine has a long duration of action (half life=8-35 h) and reaches peak plasma concentration between 6 and 8 hour with a slow onset of action.[36,37] Since both antiemetics were administered 30 min prior to the administration of the discussed emetogens, it is likely that amlodipine may not have had sufficient time to reach its sites of action, thus having lower potency. In addition, the positively charged amlodipine associates more slowly with the L-type Ca^{2+} channel, which can lead to a more gradual onset of antagonism.[38]

Unlike the above tested emetogens which can evoke vomiting within minutes of administration, cisplatin (10 mg, i.p.) requires more exposure time (30-45 min) to begin to induce emesis in the least shrew since only its metabolites are emetogenic.[39] Lack of antiemetic action of nifedipine *versus* the efficacy of amlodipine in reducing the frequency of cisplatin-induced vomiting by 80%[28,33] could be explained in terms of amlodipine having more exposure time not only to reach its sites of action, but also to compensate for its slower receptor binding kinetics. Another potential contributing factor for the efficacy of amlodipine against cisplatin-induced vomiting is its ability to bind an additional Ca^{2+} site.[31]

The discussed broad-spectrum antiemetic efficacy of nifedipine and amlodipine in the least shrew is further supported by scant available clinical case reports in which the LTCC antagonist flunarizine was shown to reduce cyclic vomiting on acute basis in one patient[40] and prophylactically in 8 other patients.[41] In addition, intracerebroventricular microinjection of nitrendipine has been shown to attenuate nicotine-induced vomiting in the cat.[42] More importantly, LTCCs appear to attenuate blood pressure to normal basal levels in hypertensive animals and patients, but do not affect the blood pressure of normotensive animals and patients.[43-45] Thus, the broad-spectrum antiemetic potential of both nifedipine and amlodipine against the diverse selective and non-selective emetogens in the least shrew further supports our proposed Ca^{2+} hypothesis and warrants initiation of clinical trials for determination of clinically-useful LTCC antagonist antiemetics.

CROSS-TALK BETWEEN LTCCS AND $5HT_3RS$

Recently we have found that the second generation 5-HT_3 receptor antagonist palonosetron (Rojas and Slusher, 2012), can suppress the ability of FPL 64176 to cause vomiting in the least shrew in a dose-dependent and potent manner.[28] Indeed, complete blockade of 2-Me-5-HT-induced vomiting was achieved at 10 mg/kg dose of nifedipine, whereas a 10 mg/kg dose of potent and selective 5-HT_3 receptor antagonists such as tropisetron,[47] or palonosetron, could not provide such complete protection against 2-Me-5-HT-induced vomiting in least shrews under similar experimental conditions.[28] These findings suggest that FPL 64176, 2-Me-5-HT, or serotonin, probably drive extracellular Ca^{2+} through both L-type- and 5-HT_3 receptor-ion channels; and/or ligands of both proteins may interact with each other's binding site. In fact Hargreaves et al[6] have demonstrated that members of all three major classes of L-type Ca^{2+} antagonists can reverse the ability of the 5-HT_3 receptor-selective agonist 1-(m-chlorophenyl)-biguanide to increase intracellular Ca^{2+} concentration in cell lines that possess either one or both of these Ca^{2+}-ion channels. The latter interaction seems not to be competitive since the binding site for the different classes of L-type Ca^{2+} channel antagonists appear not to be the same as the serotonin 5-HT_3 binding site itself (i.e. the orthosteric site) but instead, is an allosteric site in the 5-HT_3 receptor channel complex. Furthermore, 5-HT release from Enterochromaffin (EC) cells can be prevented by antagonists of both 5-HT_3 receptors and LTCCs.[48,49] Moreover, human duodenal EC cell exposure to FPL 64176 not only increases intracellular Ca^{2+} concentration but can also release 5-HT from these cells,[50] which is a Ca^{2+}-dependent process.[51] These findings provide possible mechanisms *via* which blockers of both LTCCs and 5-HT_3 receptors can mutually pre-

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vent the biochemical and behavioral effects of their corresponding selective agonists, including the vomiting behavior.

Indeed, we have further demonstrated that when non-effective antiemetic doses of nifedipine and palonosetron are combined,[28] the combination significantly and in additive manner attenuate both the frequency and the percentage of shrews vomiting in response to either FPL 64176 or 2-Me-5-HT. Furthermore, although nifedipine alone up to 20 mg/kg dose failed to protect shrews from acute cisplatin-induced vomiting, its 0.5 mg/kg dose, significantly potentiated the antiemetic efficacy of a non-effective (0.025 mg/kg) as well as a semi-effective (0.5 mg/kg) dose of palonosetron. In another study we also utilized a combination of non-effective doses of amlodipine (0.5 mg/kg or 1 mg/kg) with a non- or semi-effective dose of the 5-HT_3R antagonist palonosetron (0.05 or 0.5 mg/kg).[33] The combined antiemetic doses produced a similar additive efficacy against vomiting induced by either FPL 64176 or cisplatin. In fact relative to each antagonist alone, the combination was at least 4 times more potent in reducing the vomit frequency and provided more protection against FPL 64176-induced vomiting. The observed additive antiemetic efficacy of a combination of 5-HT_3- (and/or possibly NK_1-) with L-type Ca^{2+} channel-antagonists in the least shrew suggests that such a combination should provide greater emesis protection in cancer patients receiving chemotherapy in a manner similar to that reported between 5-HT_3- and NK_1-receptor antagonists both in the laboratory[47,52] and in the clinic.[53] Although in our investigation, the mechanism underlying the additive antiemetic efficacy of combined low doses of L-type Ca^{2+} channel antagonists with 5-HT_3R antagonists was not directly studied, the published literature points to their interaction at the signal transduction level involving Ca^{2+}.[6,54,55]

INTRACELLULAR CA^{2+} CHANNELS ANDEMESIS

The Sarcoplasmic/Endoplasmic Reticulum Ca^{2+}-ATPase (SERCA) pump is a major mechanism that transports free cytoplasmic Ca^{2+} into the lumen of Sarcoplasmic/Endoplasmic Reticulum (SER) to fill its internal Ca^{2+} stores (Figure 1).[56-58] Intracellular Ca^{2+} release from the SER into the cytoplasm is accomplished by Inositol Trisphosphate Receptors (IP_3Rs) and Ryanodine Receptors (RyRs), and this loss is counter-balanced by continuous Ca^{2+} uptake from the cytoplasm into these SER stores by SERCAs (Figure 1).[57]

Ca^{2+}-Mediated Thapsigargin-Evoked Emetic Responses

The Ca^{2+} mobilizing agent thapsigargin is a specific and potent inhibitor of SERCA pumps and also causes internal release of stored Ca^{2+} and consequently a depletion of luminal SER Ca^{2+} leading to a rise in the free concentration of cytosolic Ca^{2+} (Figure 1).[59-61] Pharmacological emptying of SER Ca^{2+} pools by thapsigargin-like drugs can trigger extracellular Ca^{2+} influx *via* activation of Store-Operated Ca^{2+} Entry (SOCE) mediated by Ca^{2+} Release-Activated Channels (CRAC) and canonical Transient Receptor Potential Channels (TRPC) in non-excitable cells, in which Stromal interacting molecule 1 (STIM1) protein functions as a sensor for Ca^{2+} store depletion.[62-64] SOCE is also functional in neurons.[65]

Our more recent studies have demonstrated that intraperitoneal administration of thapsigargin (0.1-10 mg/kg, i.p.) can evoke vomiting in the least shrew in a dose-dependent, but bell-shaped manner, with maximal efficacy at 0.5 mg/kg. Such bell-shaped emetic dose-response effect is not unique to thapsigargin since other emetogens may induce a similar dose-response effect.[28,66,67] An important consideration for the emetic effects of thapsigargin is that it augments the cytosolic levels of free Ca^{2+} in diverse tissues (e.g. muscle, neurons, mast cells, macrophages, etc.). A major role for the involvement of SOCE in the induced emesis can be discounted since the potent and selective SOCE inhibitor YM-58483, only caused a significant

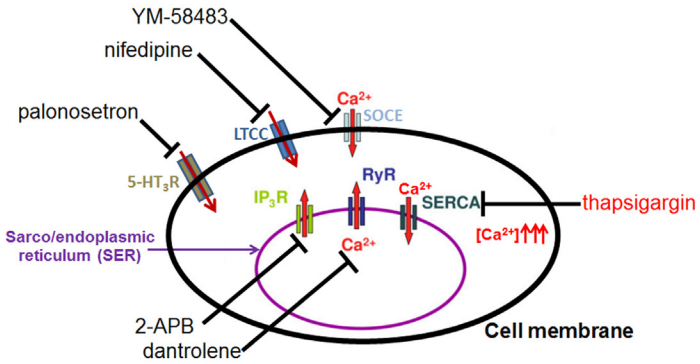

Figure 1: Summary of extracellular and intracellular calcium (Ca^{2+}) ion-channels and corresponding modulators involved in vomiting. Extracellular Ca^{2+}influx can increase cytoplasmic Ca^{2+} levels through numerous Ca^{2+} channels located in the plasma membrane including emetic L-type Ca^{2+} channels (LTCCs), serotonin 5-HT_3 receptors (5-HT_3Rs) and possibly store-operated Ca^{2+} channels (SOCE). Cytosolic Ca^{2+} concentration can be also increased via intracellular luminal release from the sarco/endoplasmic reticulum (SER) Ca^{2+} stores through the inositol triphosphate receptors (IP_3Rs) and ryanodine receptors (RyRs). This luminal Ca^{2+} loss is countere-balanced by continuous Ca^{2+} uptake from the cytoplasm into SER stores by the SER Ca^{2+}-ATPase pump (SERCA). Thapsigargin is a specific inhibitor of SERCA and thus enhances cytosolic levels of Ca^{2+}. Examples of blockers/inhibitors of corresponding Ca^{2+} channels located on the cell membrane (nifedipine, palonosetron and YM-58483, respectively) and on the SER membrane (2-APB and dantrolene, respectively) are also shown.

reduction in the frequency of thapsigargin-evoked vomiting without providing complete emesis protection (p>0.05) even at a large dose (10 mg/kg). On the other hand, the LTCC antagonist nifedipine, completely protected 50% of shrews from thapsigargin-evoked vomiting and reduced the mean vomit frequency by 85% at 2.5 mg/kg, whereas its 5 mg/kg dose nearly completely suppressed the vomit frequency and fully protected over 90% of tested shrews. In addition, significant reductions (70-85%) in the frequency of thapsigargin-induced vomiting (but without full emesis protection) were also observed when shrews were pretreated with antagonists of either IP_3Rs (2-APB at 1-2.5, but not 5 mg/kg)- or RyRs (dantrolene at 2.5-5 mg/kg)-ER luminal Ca^{2+} release channels. Moreover, while a mixture of 2-APB (1 mg/kg) and dantroline (2.5 mk/kg) did not offer additional protection than what was afforded when each drug administered alone, a combination of the latter doses of 2-APB plus dantrolene with a 2.5 mg/kg dose of nifedipine, led to a complete elimination of thapsigargin-evoked vomiting. The role of the discussed antagonists against the corresponding Ca^{2+} channels and emesis are summarized in Figure 2. Thus, our latest behavioral findings provide *in vivo* evidence that the SERCA inhibiting agent thapsigargin may enhance cytoplasmic Ca^{2+} concentration *via* inhibition of cytoplasmic Ca^{2+} uptake in the SER and Ca^{2+} store release through IP_3Rs and RyRs, as well as extracellular Ca^{2+} entry mainly through LTCCs.

Involvement of Ca^{2+} Release Channels in 5-Ht_3r-Mediated Emesis

A functional and physical linkage between LTCC and RyRs appear to exist which plays an important role in intracellular Ca^{2+} release following voltage-dependent Ca^{2+} entry through L-type Ca^{2+} channels.[68,69] We initially determined whether 2-Me-5-HT-induced vomiting can be differentially modulated *via* manipulation of IP_3Rs and RyRs.[70] We found that the 5-HT_3R-mediated vomiting was insensitive to the IP_3R antagonist 2-APB, but in contrast, was dose-dependently suppressed by the RyR antagonist, dantrolene. Furthermore, a combination of the semi-effective doses of amlodipine and dantrolene, was more potent than each antagonist being tested alone. These behavioral findings suggest that 5-HT_3R stimulation drives extracellular Ca^{2+} through L-type Ca^{2+} channels and 5-HT_3Rs, which leads to Calcium-Induced Calcium-Release (CICR) from intracellular SER stores *via* RyRs, which greatly amplifies free Ca^{2+} levels in the cytoplasm (Figure 3). These *in vivo* findings are consistent with previously published *in vitro* cellular studies demonstrating that 5-HT_3R activation evokes extracellular Ca^{2+} entry which then triggers such Ca^{2+} release from intracellular stores in a RyRs-sensitive manner.[8]

CA^{2+}-RELATED SIGNALING PATHWAY IN EMESIS

cAMP-PKA

The adenylyl cyclase/cAMP/Protein Kinase A (PKA) signaling pathway can phosphorylate both Ca^{2+} ion channels on plasma membrane and intracellular endoplasmic IP_3 receptors, and respectively increases extracellular Ca^{2+} influx and intracellular Ca^{2+} release.[71] The emetic role of cAMP in the PKA pathway is well established since microinjection of cAMP analogs

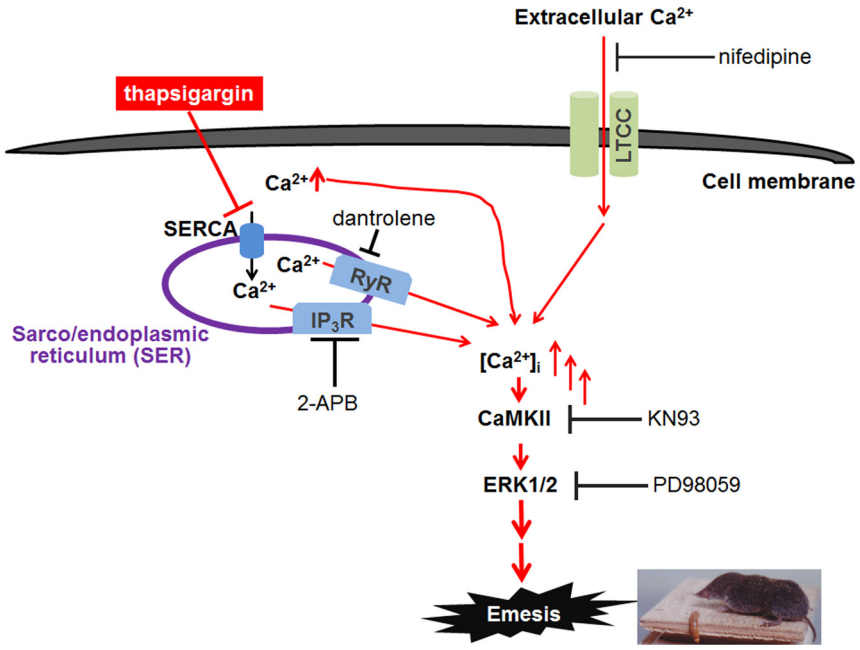

Figure 2: Schemtic model of the proposed Ca^{2+}-CaMKII-ERK1/2 signaling mechanisms in the brainstem underlying thapsigargin-induced emesis in the least shrew. Thapsigargin augments cytoplasmic concentration of Ca^{2+} *via* the: i) inhibition of cytosolic Ca^{2+} uptake into the Endoplasmic Reticulum (ER) by blocking SERCA, ii) release of stored Ca^{2+} from the ER through IP_3Rs and RyRs, and iii) activation of extracellular Ca^{2+} entry mainly through LTCCs. The induced rise in cytosolic Ca^{2+} results in CaMKII activation and subsequent ERK1/2 signaling. The LTCC blocker nifedipine, the RyR antagonist dantrolene, the IP_3R blocker 2-APB, the CaMKII inhibitor KN93, and the ERK inhibitor PD98059, respectively exhibit anti-emetic efficacy against thapsigargin-induced vomiting.

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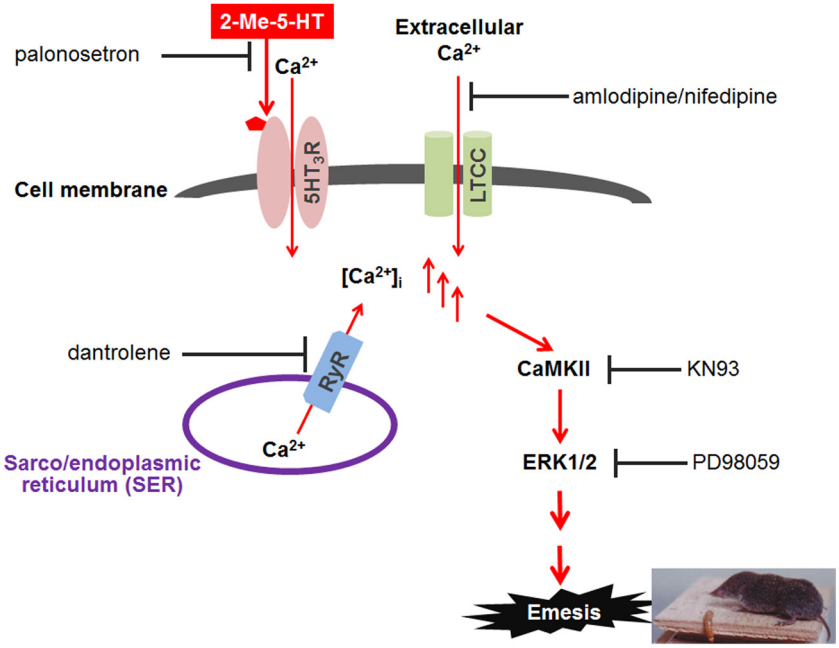

Figure 3: Schemtic model for the proposed Ca^{2+}-CaMKII-ERK1/2 signaling cascade in brainstem underlying 2-Me-5-HT-induced emesis in the least shrew. 5-HT_3R stimulation by the selective agonist 2-Me-5-HT causes an influx of extracellular Ca^{2+} through 5-HT_3Rs/L-type Ca^{2+} channels (LTCCs) which increases the free cytoplasmic concentration of Ca^{2+}, thereby-promoting luminalCa^{2+} release from the endoplasmic reticulum (ER) stores into the cytosol through ryanodine receptors (RyRs) via calcium-induced calcium-release (CICR). This elevation in cellular Ca^{2+} level leads to CaMKII activation and subsequent ERK1/2 signaling. The 5-HT_3R antagonist palonosetron, LTCC blockers amlodipine or nifedipine, the RyR inhibitor dantrolene, the CaMKII inhibitor KN93, and the ERK inhibitor PD98059, respectively exhibit anti-emetic efficacy against 2-Me-5-HT-induced vomiting.

(e.g. 8-bromocAMP) or forskolin (to increase endogenous levels of cAMP) in the area of postrema not only increase electrical activity of local neurons but can also induce vomiting in dogs.[72] Moreover, administration of 8-chloroc AMP in cancer patients produces nausea and vomiting.[73] Furthermore, use of phosphodiesterase inhibitors (such as rolipram) increase cAMP tissue levels, which consequently causes excessive nausea and vomiting in both vomit competent animals and humans.[74] We have also demonstrated that increased PKA-phosphorylation is associated with peak vomit frequency during both immediate and delayed phases of vomiting caused by either cisplatin or cyclophosphamide in the least shrew.[52,54,75]

Ca^{2+}/Calmodulin-Dependent Protein Kinase II (CaMKII) and Extracellular Signal-Regulated Protein Kinase (ERK1/2)

We have established the post-receptor emetic signaling pathway for selective 5-HT_3R agonist 2-Me-5-HT in the least shrew. As shown in Figure 3, we have proposed that following 5-HT_3R activation, the enhanced Ca^{2+} mobilization is also sequentially linked to the intracellular activation of the CaMKII-ERK1/2 pathway in the brainstem, which plays an important role in 2-Me-5-HT-induced vomiting.[70] In addition, pharmacological elevation of intracellular Ca^{2+} by systemic thapsigargin administration (0.5 mg/kg, i.p.) can also activate the emeticCaMKII-ERK1/2 signaling in the shrew brainstem[76] (Figure 2). Further support for the involvement of CaMKII-ERK1/2 pathway in thapsigargin-evoked vomiting comes from the ability of their specific inhibitors (KN93 and PD98059, respectively) to suppress the induced vomiting in a manner similar to the discussed pathway for the 2-Me-5-HT-induced vomiting.[70] In addition, the low dose combination of nifedipine, 2-APB and dantrolene, which completely abolished thapsigargin-evoked vomiting, also fully suppressed CaMKII-ERK1/2 signaling to basal levels, indicating that elevation in the cytosolic Ca^{2+} concentration is one of the earliest and requisite events in the signal transduction pathways explored in this study (Figure 2). Hence the Ca^{2+}-CaMKII-ERK1/2 emetic cascade in brainstem emetic nuclei may have a common role in the regulation of emetic responses elicited by diverse emetogens. This raises the possibility of novel therapeutic approaches in the prevention of emetic events through strategies targeting specific mechanisms linking Ca^{2+} to downstream intracellular signal transduction system(s).

CONCLUSION

In this review, we have discussed: 1) the transmission of emetic signals at the brainstem level is crucially dependent on Ca^{2+} channels located on plasma membrane and intracellular Ca^{2+} stores in the SER; 2) the implications of these findings for the design of novel therapeutic strategies and have compared the role of L-type Ca^{2+} channels antagonists nifedipine with amlodipine in emesis management; and 3) the Ca^{2+}-mediated signaling transduction pathway in the brainstem involved in diverse emetogens-evoked vomiting. We envisage development of universal antiemetics can be possible if one targets: i) one

critical step in each of the few available post-receptor emetic signal transduction systems which the above-discussed diverse emetogens share downstream of their corresponding receptors, or ii) a common essential signal which can cross-talk between these transduction pathways such as, Ca^{2+}.

CONFLICTS OF INTERESTS

The authors declare that they have no conflicts of interest.

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A Multicenter UK Study on Trainee Involvement in Clinical Audit: Is it an Effective Contribution to Service Quality Improvement or a Portfolio Generating Activity?

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ABSTRACT

Aims: The primary purpose of audit is to improve quality of care, but it is also considered educationally valuable. Audits are often sought in job applications and also form annual review targets. The study aimed to examine audit activity across hospital trainees.
Methods: 100 doctors, ranging from F1 to Specialty Training year 5 (ST5) level across 10 UK hospitals were invited to complete a printed or online questionnaire about audit involvement.
Results: Seventy five (75%) participated, including 1 F1 (1.3%), 34 F2s (45%), 6 ST1s (8%), 14 ST2s (19%), and 20 ST3-5s and post-basic training fellows (26%). Their Specialities included: Medicine 33(44%), Surgery 29(38%), General Practice (GP) 6(8%), Anaesthesia 4(5.3%), Accident and Emergency (A&E) 2(2.6%) and Ophthalmology 1(1.3%). Seventy (93%) claimed audit involvement in the last year. Most (54, 72%) worked by themselves, with over a quarter led by others (28%). None received audit training. Most (86%) completed within 6 months. Audits focused chiefly on local practice (96%), with only 3 regional or national audits (4%). Only five were re-audits (6.7%), and just four were submitted for publication (5.3%). Most (60, 80%) were formally presented: 46 at local meetings (61%), 10 reaching regional (13%) and 4 international (5.3%) conferences.
Conclusion: The positive response rate indicates that audit is a frequent trainee activity, but the results suggest that it is mainly a self-directed portfolio fulfilling exercise. Improved training and supervision may be needed to achieve the primary aim of audit, which is improved clinical practice, whilst the educational value is unproven.

KEYWORDS: Audit; Portfolio; Doctors.

ABBREVIATIONS: A&E: Accident and Emergency; GP: General Practice; NHS: National Health Service; DOH: Department of Health; COG: Clinical Outcome Group; GMC: General Medical Council; MDU: Medical Defence Union; MPS: Medical Protection Society; SPSS: Statistics is a software package used for statistical analysis; PRISM: Parameter-related Internal Standard Method; MMC: Modernising Medical Careers; EWTD: European Working Time Directives.

BACKGROUND

From the possible first ever clinical audits, undertaken by Florence Nightingale during the Crimean war of 1853-1855, to the Codman's "end result idea" in 1912 on monitoring surgical outcomes audit has come a long way and is now widely accepted as a quality improvement process and practiced within the National Health Service (NHS).[1]

Department of Health's (DOHs) White Paper *`Working for Patients'* laid down the

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plans for the need and the planning of the audit.[2] Evolution of audit in NHS in its present form, dates back to early 90`s and the first meeting of DOH`s first Clinical Outcome Group (COG) took place in 1992. The aim was to give strategic direction to the clinical rather than merely medical audit. It was the first time when a multidisciplinary team approach was adopted to improve clinical outcomes.[3]

In 1993, medical audit became clinical, clinicians across the board came together on a common platform to review patient`s clinical outcome. With further availability of resources and funding clinical audit became an accepted norm across the NHS trusts. Clinical audit is now an established part of the NHS landscape and is at the core of a local monitoring system of performance. Clinical audit was originally integrated into clinical governance systems[4,5] as one of the seven pillars, and soon after was made a component of Clinical Governance.[6,7] It was subsequently embraced by various governing bodies, The Government (our employers), The General Medical Council (GMC) (our regulatory body), our insurers (Medical Protection Society (MPS), Medical Defense Union (MDU), etc.) and our respective professional bodies.

The NHS Plan[8] further gave these policies impetus and introduced proposals for mandatory participation by all doctors in clinical audit and developments to support the involvement of other staff, including nurses, midwives, therapists and other NHS staff.

This study was conducted to identify the trends among trainees in NHS, their participation and awareness about clinical audit. We also wanted to identify areas of improvement in audit activity among trainees in UK.

MATERIALS AND METHODS

This study was carried out in accordance with UK clinical governance guidelines. Doctors ranging from F1 to ST5 level from ten hospitals in UK participated by completing online questionnaires or hand written forms. Seventy-five percent (n=75, 75%) completed questionnaires were returned.

RESULTS

Among those 75 responses, 1(1.33%) was from F1, 34(45%) were from F2s, 6(8%) were from ST1, 14(18.66%) were from ST2, and 20(26%) were from ST3-5s and post-basic training fellows. (Figure 1)

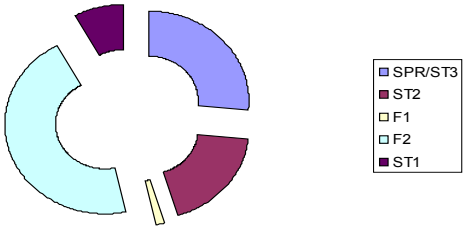

Figure 1: Responses from training fellows.

33(44%) respondents were from medicine, 29(38%) from General surgery and allied Specialities, 6(8%) from GP rotation, 4(5.3%) from anaesthesia, 2(2.6%) from A&E and 1(1.33%) from ophthalmology. (Figure 2)

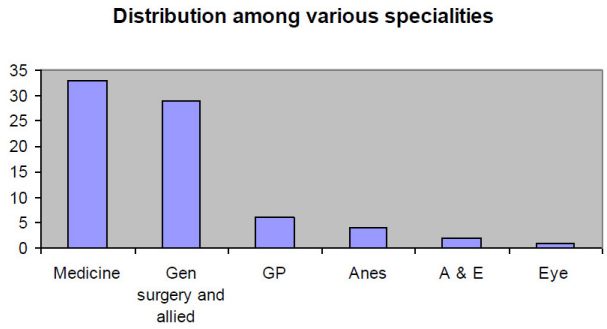

Figure 2: Distribution among various specialities.

About 70 respondents (93.3%) had been involved in audit in last 12 months of their job across all the Specialities. Most (54, 72%) of the respondents did audit on their own initiative and only about one fourth of them were motivated by others (n=21, 28%). (Figure 3)

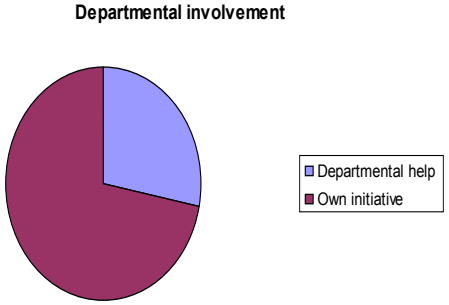

Figure 3: Involvement of various specialities.

Eighty six percent (65) of the respondents completed their audit within six months. (Figure 4)

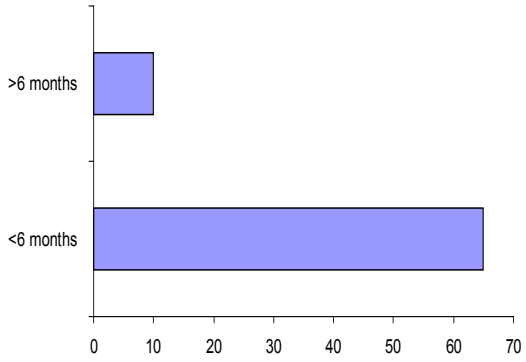

Figure 4: Completion of audit.

Only 6.66% (n=5) of the audit topics were related to the re-audit part of the audit loop. (Figure 5)

Only four respondents (5.33%) manage to submit it for

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publication. (Figure 6)

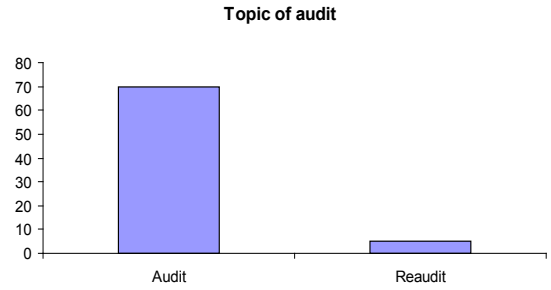

Figure 5: Topics were related to the re-audit.

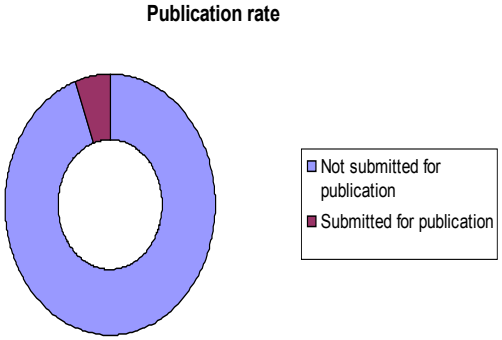

Figure 6: Publication rate.

Most of the audits (n=60, 80%) were presented at a local (n=46, 76.66%), regional (n=10, 16.66%) international (n=4, 6.66%) and none of the audits were presented on national forum. (Figure 7)

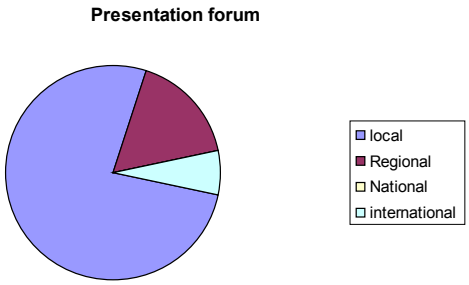

Figure 7: Presentation of different forums.

Most of the audits were focused on local practices within their own institution (n=71, 96%) and only 4% of the respondents were involved in regional and national audits. Very few respondents (1.3%) were using advanced statistical software like Statistics is a software package used for statistical analysis (SPSS) and Parameter-related Internal Standard Method (PRISM).

DISCUSSION

Audit has always been considered as a key component in improving medical education and training. It has been suggested as a vital part of emergency medical education.[9]

Modernising Medical Careers (MMC) or European Working Time Directives (EWTD) in conjunction has lead to shorter training period, wanting people short of time to do academic/clinical governance activities. However, undertaking such activities is always beneficial and leaves a person with reflective education.

It cannot be overemphasized the importance of audit activity in clinical career and the same can be achieved by simple audit exercises better methods and appropriate guidance.[10]

Medical trainees have always been questioning about the educational value of audit activity and it creates subconscious resentments towards fulfilling audit activity and the same impression is carried on as being a consultant and thereby undermining the clinical significance of audit activity.[11]

We are already aware of the fact that most of the trainee doctors are involved in audit activities but the need to have better education and training about audit practices has been emphasized time and time again.[12] Vast majority of clinical audits conducted by junior doctors don't have significant clinical impact in terms of change of practice purely due to wont of quality of conducted audit and inadequate skilled clinical supervision.[12]

Nettleton J et al have reported experience of 146 junior doctor's across 21 Specialities about clinical audit and have suggested that although enthusiasm was abundant, however falling short of core knowledge and methodology of audit and therefore failing to have robust framework for undertaking effective audit for a meaningful result which may reflect in change of clinical practice.[13]

Karran et al in 1993 have reviewed the perception of general surgical staff within the Wessex region of the status of quality assurance and surgical audit and they inferred that majority of registrars (86%) agreed the importance of collection of relevant, accurate and complete clinical outcome.[14] However, 56% among them realized that that the primary objectives were not met. The reply from the consultants was in agreement with meeting meaningful surgical audit and quality assurance, which should be ideally critically peer reviewed.[14] Brazil et al have looked into audit as a learning tool in postgraduate emergency medicine training.[9]

Our study suggests that re-audits were rarely carried out, causing audit cycles to be incomplete. We have also identified that we need to encourage the trainees to use the latest available statistical software's, so that they can appreciate the value of having scientifically robust approach and to be in a better position to critically appraise any recent advancements in our profession. Most of the junior doctors are motivated to do the audit on their own initiative but we need to better educate them in all aspects of auditing practices including presentation of audit results at national level and to encourage them to publish it. Better education will ensure that audits produce useful recommendations to further improve clinical governance. Early cultivation of

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good auditing practices is particularly important amongst junior doctors so that they in turn can educate their juniors as their careers progress.

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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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