

Radiation Induced Diarrhoea – Literature Review

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ABSTRACT

Radiation-induced diarrhoea is an acute side effect of radiotherapy treatment to the pelvic area, experienced by nearly all patients. This paper will explore the patho-physiological rationale of diarrhoea, the causes of radiation-induced diarrhoea, the factors that influence the severity and occurrence, and the treatment of diarrhoea in relation to the radiotherapy setting, by analysing the current literature and will conclude by outlining future directions in this field.

INTRODUCTION

Radiation-induced diarrhoea, may be an acute side effect of radiotherapy treatment to the pelvic area.¹⁻¹⁶ While radiation-induced diarrhoea is a well known sequel of radiotherapy, the patho-physiology of the effect that it has on the gastrointestinal tract is both poorly defined and understood.^{1,14-18} The effects of radiation exposure to the gastrointestinal tract dates back to 1897, when Walsh reported that radiation caused inflammation of the mucous membranes.¹⁹

MacNaughton, (2000), states that the radiation causes mucosal dysfunction, due to the effects on the epithelial stem cell cycle in the crypts of the intestine. He also states that this inhibition of epithelial mitosis, in combination with the loss of mitotic function, can result in the loss of water, protein and electrolytes, which in turn may leave the gut permeable to bacteria which may increase mucosal inflammation.⁹

Somosy, Horvath, Telbisz, et al, (2002), also describe radiation-induced diarrhoea as an electrolyte imbalance due to the effects on the cellular transport process, and to the secondary actions of bile salts on the mucosa of the intestine, the loss of absorptive cells, the denudation of the intestinal villi and the subsequent changes of the gastrointestinal blood flow.¹⁴ The authors also agree with MacNaughton, by stating that the loss of intestinal mucosal integrity may lead to endotoxemia and bacteremia.

The National Cancer Institute, (NCI), (2000), states that the necrosis of crypt wall cells can start within a day of receiving a dose of up to 300cGy, with increased symptoms occurring with further treatment, as the functions of the gastrointestinal tract are altered or lost.¹⁰ Somosy, Horvath, Telbisz, et al, (2002), stated that the ratio of the enteroendocrine, Paneth cells and differentiated enterocytes were also altered 2-4 days post-irradiation. The author also goes further to say that if the symptoms are left untreated, they can cause death within two weeks,¹⁴ however death due to gastrointestinal injury is uncommon unless high doses and large fields are treated, in which case late effects are more likely to occur.

Causes of diarrhoea

There are many causes of diarrhoea including viral and bacterial infection, drug-induced from antibiotics and chemotherapy,

as well as cellular and biochemical processes. These processes include intestinal ion secretion, unusual amounts of osmotically active solutes that are poorly absorbed, inflammatory exudation of protein, blood and mucous, abnormal intestinal mobility and stimulation of ion secretion which inhibits normal ion absorption.⁷ The later is also known as secretory diarrhoea and is the common type associated with cancer treatments.

Radiation-induced diarrhoea results from the disruption of immature stem cells secreting fluid into the lumen and the inhibition of mucosal absorption of the fluid by the villi, causing increased fluid and electrolytes in the lumen, which peaks 1-2 weeks post-irradiation.⁴ The radiation causes mucosal crypt-cell aberrations, including: reduced circumference of the crypts; shortened villi length; vertical, horizontal, lateral and rudimentary collapse of villi, as well as cell degradation and epithelial flattening.^{4,11,14} Rubio, (1996), noted histological changes such as the structural changes in the crypts, loss of Paneth and goblet cells and cell necrosis when he irradiated the small intestines of rats.² Vignuelle, Rao, Fasano et al, (2002), also reported the same functional and structural changes occurred in the intestinal mucosa of irradiated Rhesus monkeys, however it is difficult to correlate animal findings to human studies.¹⁵

Factors that influence the severity and occurrence of diarrhoea

There are many factors that can influence the severity and duration of radiation-induced diarrhoea. The first factor is the dose and fractionation of the radiation given. Generally, if the daily and total dose given to the intestines is high, the greater the risk of radiation-induced diarrhoea.¹⁰ Symptoms of radiation-induced diarrhoea are usually seen after an accumulated dose of 18-22Gy is reached using conventional fractionation.^{3,5,12,20,22}

The second factor is that the volume of normal small or large bowel and rectum irradiated will also increase the severity and risk of radiation-induced diarrhoea.^{10,21} It is also important to note that if a large volume of gut is treated, that as well as the patient experiencing acute radiation-induced diarrhoea, approximately five per cent of patients will go on to experience chronic radiation damage.²³ For this reason it is essential to limit the amount of small bowel in the treatment area by incorporating small bowel contrast with CT planning techniques.

Thirdly, if the patient is having concurrent chemotherapy and radiotherapy, the frequency and severity of the radiation-induced diarrhoea is increased.^{6,10} Gallagher, (1999), and Ippoliti, (1998), both state that 5-fluorouracil, (5-FU), used alone was a common cause of clinical diarrhoea, and when used in combination with other chemotherapy drugs resulted in a high percentage of patients requiring hospital admission due to the severity of their symptoms.^{7,4} Miller, Martenson, Sargent, et

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al, (1998), also state that the combination of 5-FU with pelvic radiotherapy increases acute gastrointestinal toxicity, including an increased occurrence and severity of diarrhoea.⁵ This is a major concern in radiotherapy, as many upper GI tract and pelvic treatment protocols include the administration of concurrent 5-FU chemotherapy during the first and last weeks of the radiotherapy treatment.

Finally, the patient's prior medical history can also influence the degree to which radiation-induced diarrhoea is experienced. Patients who have had prior abdominal surgery, pelvic inflammatory disease or diverticulitis, or have other comorbidities such as inflammatory bowel disease such as Crohn's or ulcerative colitis, have a greater risk of experiencing side-effects from radiotherapy as they already have a lower tolerance.^{7,10}

Treatment of diarrhoea

Just as there are many causes and factors influencing radiation-induced diarrhoea, there are also many treatments for the prevention and control of the associated symptoms. These include anti-diarrhoeal drugs, maintaining intestinal integrity, diet and nutrition, prevention by methods such as treatment planning, field positioning, and treatment sequencing. All of these factors will now be addressed in turn.

Anti-diarrhoeal drugs are an important part of the control of radiation-induced diarrhoea and are generally classified by their mechanism of action, for example; intraluminal agents, proabsorptive agents, intestinal transit inhibitors, and antisecretory drugs.^{4,7} Intraluminal agents, such as activated charcoal have been used as anti-diarrhoeal agents for a long time, however they are unsuitable for cancer patients as they can interfere with the absorption of other oral anti-diarrhoeal medications. Cholestyramine has been found to be effective for controlling radiation-induced diarrhoea in patients having radiation therapy. Proabsorptive agents such as clonidine inhibit secretion and stimulate absorption in the intestine, however its use is restricted to those patients who do not have hypotension.⁴

Intestinal transit inhibitors including loperamide, (Imodium), diphenoxylate, (Lomotil), and opioids are frequently used to control radiation-induced diarrhoea, as they slow down intestinal motility by decreasing the amount of acetylcholine released by the efferent nerve endings from the gut that control motility.^{1,4,5,10,12,24} In the study by Vigneulle, Rao, Fasano et al, (2002), they found that radiation-induced diarrhoea occurred after 4-5 days of abdominal radiotherapy, at which point Imodium was used to treat the symptoms, however this treatment was changed to Lomotil for three days if the diarrhoea persisted. This drug sequence was continued until asymptomatic. While this regime was used on rhesus monkeys, it has been used clinically on patients receiving pelvic radiotherapy.¹⁵ Currently, the use of anti-motility agents such as Imodium and Lomotil are considered the treatment of choice for radiation induced diarrhoea in Australia.

An antisecretory drug named octreotide, reduces diarrhoea by inhibiting the exocrine and neuroendocrine secretions and small intestine motility, and by increasing electrolyte and water absorption.⁴ Octreotide has been shown by Gebbia, Carreca, Testa et al, 1993, to produce remission of diarrhoea in 80 per cent of patients having 5-FU chemotherapy as opposed to only 30 per cent of patients receiving Imodium. This study also highlighted the fact that when comparing agents, the route of administration, dosage and duration must be taken into consideration.²⁵ Clinical studies have shown that patients that are being treated with 5-FU and cisplatin chemotherapy, who receive a continu-

ous intravenous infusion of octreotide, have complete resolution of their severe diarrhoea. Similar results were found in patients with colorectal cancer who were treated with 5-FU and leucovorin.⁴

While octreotide has been proven as being effective in chemotherapy-induced diarrhoea, there were no pilot studies or controlled clinical studies until 2002, when Yavuz, Yavuz, Aydin, et al, conducted an open, prospective randomised trial to assess the effectiveness of octreotide on patients suffering diarrhoea as a side-effect of pelvic radiotherapy.¹² The authors concluded that octreotide was a safe and effective alternate drug to control moderate to severe radiation-induced diarrhoea, which helped symptoms enough to avoid undesirable interruptions of treatment. They also concluded that it would be a treatment of choice for patients undergoing combined chemotherapy and radiotherapy protocols. The study identified the need for a double blind, placebo-controlled trial for patients receiving pelvic irradiation, to further evaluate the role of octreotide in preventing acute and chronic radiation-induced diarrhoea, and is currently being undertaken by the authors. Although octreotide has efficacy in treating established radiation enteritis, it has not been approved for this use in Australia. Octreotide is also very expensive and administered by injection, making it an inappropriate choice in a prophylactic situation.

Tropisetron is a serotonin-receptor antagonist that is currently being studied for the treatment of radiation-induced diarrhoea.⁴ Dincer, Bilge & Tmaz, (1995), conducted a controlled pilot study to evaluate the antiemetic and anti-diarrhoeic effects of oral tropisetron in patients undergoing pelvic radiotherapy.²⁶ They concluded that oral tropisetron is effective for the prophylactic treatment of nausea, vomiting and diarrhoea. Miller, Martenson, Sargent et al (1998), contradict this by stating that prophylactic anti-diarrhoeal medication should be avoided as it can cause constipation.⁵

Another drug that has been administered prophylactically is the 5HT₃ receptor antagonist Granisteron. Research conducted by Krantis, Rana & Harding, (1996), showed that it was both effective in preventing an increase in radiation-induced pellet expulsion and in slowing down the rate of expulsion in guinea pigs.²⁷ Studies in human volunteers have shown that Granisteron modulates intestinal motility, however it does cause mild constipation and hypomotility, which is not ideal according to Miller, Martenson, Sargent et al (1998).

Several other drugs have been trialled for the treatment of radiation-induced diarrhoea. One of these drugs was olsalazine, which is designed to deliver 5-aminosalicylate to the bowel with little systemic absorption. Olsalazine was trialled in Great Britain using a randomised, double-blind clinical trial for patients having pelvic irradiation. The results concluded that administering the drug actually increased both the incidence and the severity of radiation-induced diarrhoea and therefore its use during pelvic radiotherapy is now contraindicated.³

Henriksson, Franzen, & Littbrand, (1992), and Henriksson, Arevan, Franzen, et al (1990), both conducted randomised trials and suggested that sucralfate, a sulfated sucrose compound, may be effective in preventing radiation-induced diarrhoea for patients undergoing pelvic radiotherapy as it increased stool consistency and decreased stool frequency.^{28, 29} Henriksson, Franzen, & Littbrand, (1992), also speculated that the drug formed a protective barrier on the denuded intestinal mucosa from enzymes, acids and bacteria.

In 1997, O'Brien, Franklin, Dear, et al investigated the use of sucralfate given rectally to prevent acute radiation proctitis.

Their study concluded that a daily enema of sucralfate did not substantially reduce radiation proctitis symptoms and did not recommend its routine clinical use.³⁰ In 2002, they followed up the patients in the initial study and whilst they found an association between acute and late toxicity, they confirmed that rectal sucralfate was not effective in reducing late radiation injury.³¹

In 1998, Martenson, Bollinger, Sloan, et al, as part of the North Central Cancer Treatment Group (NCCTG), conducted a multi-institutional trial of sucralfate on patients undergoing pelvic radiotherapy and concluded that it did not prevent bowel toxicity and that the conflicting results indicated the need for further studies.³² In 2001, Australian researchers Kneebone, Mameghan, Bolin, et al concluded that oral sucralfate did not improve the symptoms of acute radiation proctitis when taken prophylactically during radiotherapy, which confirmed the previous findings by NCCTG.³³

Sulphasalazine is a drug that inhibits both the synthesis of eicosanoids in the intestinal mucosa, and the lipoygenase and cyclooxygenase pathways in the metabolism of arachidonic acid, and has been successfully used in the treatment of ulcerative colitis.⁸ Although sulphasalazine had been previously trialled in a non-controlled study, Kilic, Egehan, Ozenirler et al, (2000), were the first to conduct a double-blind, randomised, placebo-controlled study to evaluate the use of sulphasalazine in preventing radiation-induced diarrhoea and found that it effectively reduced the frequency and severity of diarrhoea and other related symptoms in over half of the patients. The researchers concluded that further trials are necessary to determine the late gastrointestinal toxicity of the drug.⁸

Maintaining intestinal integrity during radiotherapy influences the quality of life experienced by patients.³⁴ The intestinal mucosa obtains its supply of nutrients from the bacterial flora of the gut, however pelvic irradiation changes the vascular permeability of the intestinal mucosa and ultimately the bacterial flora. A decrease or loss of this bacterial flora and thus intestinal integrity may lead to bacteremia and endotoxemia.¹⁴ Salminen, Elomaa, Minkkinen, et al, (1988), conducted a randomised study to see if intestinal integrity could be preserved during radiotherapy by administering live lactobacillus acidophilus cultures to patients.³⁴ The results showed that the culture appeared to be effective in preventing radiation-induced diarrhoea, however they did find that flatulence was a side-effect, due to the addition of lactulose to promote lactobacillus growth in the colon, in the test group.

Delia, Sansotta, Donato, et al, (2002), also conducted a randomised pilot trial of a probiotic preparation called VSL#3 to prevent radiation-induced diarrhoea.¹³ The study found that none of the patients experienced any treatment-related toxicity and that the preparation was safe for cancer patients to use during radiotherapy, however due to the small sample size used in the trial, further studies need to be performed. The authors suggest that probiotic bacteriotherapy treatment has the potential to decrease the incidence and severity of radiation-induced diarrhoea by protecting the gastrointestinal tract from radiation injury.

Diet and nutrition also play an important role in managing radiation-induced diarrhoea, as the damage caused by the radiation affects the enzymes in the intestine. One of the main enzymes affected is lactase, which aids in the digestion of milk products. Yeoh, Horowitz, Russo et al, (1993), found that patients in their prospective longitudinal study on the effects of pelvic radiotherapy on gastrointestinal function, may benefit from the avoidance of milk products due to the high prevalence

of lactose malabsorption.¹ As mentioned previously, patients are still encouraged to eat yoghurt to promote intestinal integrity by maintaining the natural gut flora and to increase their fluid intake.^{10,34} Patients having pelvic radiotherapy are often advised to implement a low-residue, low-fat, lactose-restricted diet to prevent radiation-induced diarrhoea.^{10,35} Diet sheets are generally given to the patients either before or at the commencement of treatment so that they can modify their diet prior to the onset of the radiation-induced diarrhoea.

Prevention is often better than cure and by undertaking methods such as: surgery, treatment planning, field positioning, treatment sequencing and therapeutic ratio, the occurrence and severity of radiation-induced diarrhoea may be reduced. Surgery can be used to exclude the amount of small intestine from the radiation field, to displace small bowel and to partition the abdominal and pelvic cavities as a means to prevent acute radiation-induced diarrhoea.^{5,8} Surgery can also be used to place radiopaque clips where the tumour was to help localise the tumour bed.¹⁰

Other less invasive preventative methods include limiting the amount of small bowel in the treatment field, by using multiple beam techniques, as opposed to a parallel pair, customised shielding to block out bowel, the use of equipment such as bellyboards to displace the bowel anteriorly when treating rectal cancer, and by treating the patient with a full bladder to displace the small bowel up and out of the treatment field. Treatment planning should be done using CT or three-dimensional planning to achieve a high dose to the tumour volume, whilst limiting the dose to the surrounding organs. Modification to the treatment sequencing of surgery, chemotherapy and radiotherapy can also be used to decrease the severity of radiation-induced diarrhoea.^{5,10,21,36}

A study by Richter, Fink, Hughes, et al, (1998), suggested that by maintaining the endothelial cell anticoagulation function during pelvic radiotherapy can optimise the therapeutic ratio, as it has the potential to prevent hypoxia and radioresistance.¹⁸ Begent, Collis & Lewis, (1995), describe the use of hyperfractionation as a means of increasing the therapeutic advantage, by killing tumour cells in a reduced timeframe to prevent proliferation, whilst allowing normal tissue to repair.³⁶ They state that whilst there are no reported benefits in the use of hyperfractionation on rectal tumours, there are centres currently using this technique.

In the past, a lot of experimentation on radiation-induced diarrhoea and intestinal injury has been done on animals such as rats, guinea pigs, dogs and monkeys, and whilst this has given researchers an insight into the functional and structural changes that radiation has on the intestines, the researchers are aware of the limitations of correlating their results to humans.^{15,16,27} It is for this reason that lately there has been an increase in the number of human trials being conducted. In the future, it will be interesting to see the results from these trials, including the one currently being conducted by Yavuz, Yavuz, Aydin, et al, to evaluate the benefits of short and long acting octreotide on chronic radiation-induced diarrhoea, as this may reduce the incidence of long-term complications that currently face a small proportion of patients undergoing pelvic radiotherapy.¹²

Gallagher, (1999), suggests that retrospective data collected from cooperative group clinical trials should be further analysed so that the grade, type and duration of diarrhoea can be better defined, as this will allow oncologists to closely monitor patients considered to be of high risk of experiencing radiation-induced diarrhoea. He also recommends further study be con-

ducted on oral rehydration fluids, octreotide and oral glutamine. The later is currently being trialled by the North Central Cancer Treatment group, (NCCTG) in the United States.⁷

CONCLUSION

In conclusion it can be said that whilst radiation-induced diarrhoea is often short in duration, it can cause many symptoms that can severely impact on a patient's quality of life. These symptoms may be increased by the addition of adjuvant chemotherapy to the radiotherapy protocol, but can be managed by a combination of the drugs and preventive measures outlined in this paper. It is important that the underlying cause of the diarrhoea is assessed and other causes such as obstruction and infection, are ruled out prior to the administration of drug therapy. At present the treatment of choice for radiation-induced diarrhoea seems to be anti-motility agents such as Imodium and Lomotil, combined with a low-residue, lactose-restricted diet. The challenge for future studies is to determine the exact mechanisms that underpin radiation-induced diarrhoea, so that more effective treatment strategies can be implemented to improve the quality of life for those patients undergoing pelvic radiotherapy.

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