Safety of Enalapril after Abdominal Irradiation

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ABSTRACT

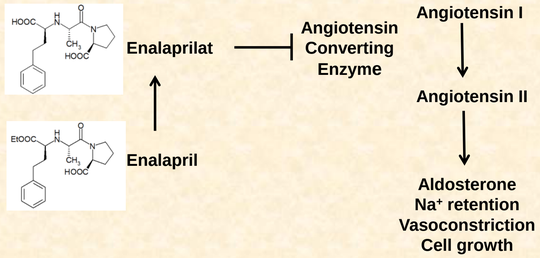
Angiotensin-converting-enzyme inhibitors (ACEi) mitigate experimental and clinical radiation injuries to kidneys, lung, and skin. Whole or partial body irradiation can expose the gastrointestinal (GI) tract. ACEi do not mitigate GI radiation injury in rats, but the GI tract is likely to be included in a radiation exposure to kidneys. Irradiation to the GI tract and tolerance of ACEi must be understood. We tested the ACEi enalaprilat, then enalapril, in a canine model. Five 20 to 25 kg dogs underwent 600 cGy abdominal irradiation. Each dog served as their own non-irradiated control. Gastrointestinal motility was assessed by surgically-placed intestinal strain gauges. Enalaprilat, 0.625 mg/kg, intravenous, twice daily, alone did not affect GI motility or animal well-being. Irradiation (rads) caused significant increases in retrograde giant contractions (RGC), giant migrating contractions (GMC), and their respective correlates, vomiting and diarrhea, within the first week after rads. Rads followed immediately by enalaprilat caused no significant change in RGCs or GMCs but all dogs in this group were clinically worse than irradiated dogs not on drug; they were euthanized within a week after rads. In a second experiment, 6 dogs also underwent 600 cGy abdominal rads, 3 were instrumented with strain gauge transducers and 3 were non-instrumented. Animals were irradiated with a single dose of 600 cGy and started enalapril 0.5 mg/kg, once a day, started one week after rads. All dogs had vomiting and diarrhea, which were maximal on the day of radiation. During the second week after rads, irradiated dogs taking enalapril were clinically well, had no vomiting or diarrhea, and their GI motility monitoring was not different from their control recordings before rads. We conclude that after abdominal irradiation, immediate use of ACEi may cause greater morbidity, but **starting ACEi at one week after abdominal x-ray exposure has no adverse effects**. This is critically important for the use of ACEi to mitigate other organ injuries, such as those to kidneys and lungs, since starting ACEi to mitigate radiation injury to lung or kidney is not needed until one week or more after irradiation. Starting ACEi within the first week of a total body exposure is not necessary and may be harmful.

BACKGROUND

We have a well established model of the prodromal effects of radiation using a canine model and an orthovoltage x-ray machine as the radiation source. In contrast to rodent models, canines vomit and have diarrhea following radiation. These effects are associated with enhanced GI motility and occur within hours of exposure, days before anatomic and histologic injury.

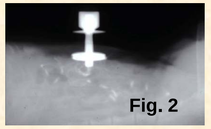
ACEi mitigate radiation induced damage to lung, kidneys and possibly skin in rodent models. The mechanism of action of ACEi is shown in Fig. 1. We sought to test ACEi as mitigators of GI injury. We also sought to test their safety for use in partial body exposures that would include kidney or lung, along with GI tract. An adverse effect of ACI on GI tract might prevent the safe use of ACEi to mitigate injuries of other organs in the radiation field.

ACE inhibitors, such as enalapril, reduce blood pressure, and mitigate lung and kidney radiation injury (Fig. 1)



METHODS

12 strain gauge transducers were implanted on the small and large intestine of dogs to record circular muscle contractions (Fig. 2). Following recovery from surgery, control recordings were made using enalaprilat, 0.625 mg/kg, intravenous, 2x/day. 600 cGy x-irradiation was given by a Pantak HF320 orthovoltage machine with 300 kV x-rays at a field size of 30x25 cm. Dogs were irradiated with parallel opposed lateral fields at a dose rate of 52 cGy/min. Dogs were sedated during radiation. In a second experiment, 6 dogs also underwent 600 cGy abdominal rads, 3 were instrumented with strain gauge transducers and 3 were non-instrumented. Animals were irradiated with a single dose of 600 cGy and started enalapril 0.5 mg/kg, once a day at one week after rads. All dogs had vomiting and diarrhea, which were maximal on the day of radiation. Instrumentation is shown in Fig. 2 and normal small intestinal contractile activity is seen in Fig. 3.



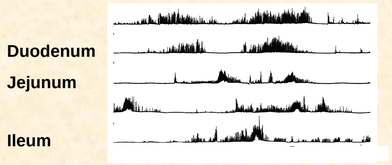


Fig. 3 *Normal contractile activity of the small intestine is shown. Contractile activity starts in the duodenum and propagates towards the ileum.*

Results

Enalaprilat, 0.625 mg/kg, intravenous, twice daily, alone did not affect GI motility or animal well-being. Irradiation caused significant increases in retrograde giant contractions (RGC, Fig. 4), giant migrating contractions (GMC), and their respective correlates, vomiting and diarrhea, within the first week after rads. GMCs are shown in Fig. 5.

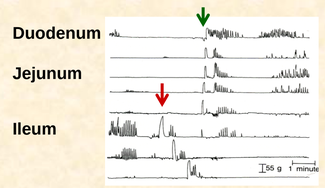


Fig. 4 *Following irradiation, there is an increase in both RGCs (green arrow)& GMCs (red arrow). RGCs begin in the mid small bowel and rapidly propel intestinal contents into the stomach immediately prior to emesis.*

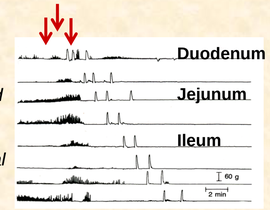


Fig. 5 *Following irradiation, 3 giant migrating contractions (GMCs, red arrows) are seen starting in the duodenum and migrate 300 cm, the entire length of the small intestine in about 5 minutes. GMCs occur in both the small intestine & colon & are associated with the rapid caudal migration of feces. When GMCs occur in the left side of the colon, they are associated with uncontrolled defecation.*

Rads followed by enalaprilat caused no significant change in RGCs or GMCs but all dogs in this group were clinically worse than irradiated dogs not on drug. Enalaprilat dogs drooled excessively, IV fluids were required each day following rads. Three of 4 dogs were sacrificed for excessive weight loss with bloody stools and vomit, symptoms not experienced by control animals.

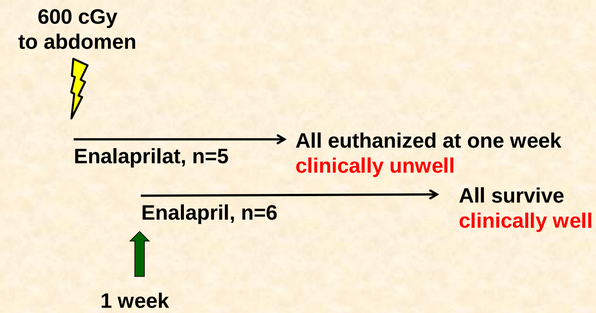
All dogs had vomiting and diarrhea, which were maximal on the day of radiation. Because of significant, unexpected morbidity of immediate initiation of ACEi, we studied a second group of animals, 3/6 were instrumented and 3/6 were uninstrumented. ACEi were started one week after rads.

Dogs starting enalapril one week after rads had no clinical symptoms. During the second week after rads, irradiated dogs taking enalapril were well, had no vomiting or diarrhea, and their GI motility monitoring was not different from their control recordings before rads. Both creatinine and blood urea nitrogen (BUN) were normal before and after rads.

DISCUSSION

ACEi are the only clinically-approved drugs that mitigate the late effects of radiation on the kidneys, lungs, skin and brain (Moulder). The present study shows that premature use of ACEi may worsen the acute effects of radiation upon the gastrointestinal tract. Our earlier studies show that the prodromal effect of radiation is caused by changes in motility (Otterson1988, 1992). Delayed administration of ACEi does not impair animal health and, based upon prior rodent studies, would be expected to mitigate the late damage of radiation on non-GI organs in a partial body radiation field.

While one would not expect the early and late effects of radiation to have the same mechanism, this is the first data which demonstrates that an effective mitigator of the late effects of radiation may actually harm the animal given during the acute phases of radiation sickness.



CONCLUSIONS

When animals had adverse reactions to ACEi, we examined whether instrumentation or timing of administration of ACEi caused the effect. We conclude that early administration of ACEi, during the prodromal phase of radiation sickness is potentially harmful. Delayed administration of the ACEi produced no ill effects on the animals, which would permit ACEi to mitigate the late effects of radiation to the kidneys, lungs and skin. After abdominal irradiation, immediate use of ACEi may enhance GI toxicity and cause greater mortality, but starting ACEi at one week after abdominal x-ray exposure has no adverse effects. This is critically important for the use of ACEi to mitigate other organ injuries, such as those to kidneys and lungs, since starting ACEi to mitigate radiation nephropathy or pneumopathy is not needed until one week or more after irradiation. Starting ACEi within the first week of a total body exposure is not necessary and may be harmful.

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