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Emesis as a Screening Diagnostic for Low Dose Rate (LDR) Total Body Radiation Exposure

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Abstract

Current radiation disaster manuals list the time-to-emesis (TE) as the key triage indicator of radiation dose. The data used to support TE recommendations were derived primarily from nearly instantaneous, high dose rate exposures as part of variable condition accident databases. To date, there has not been a systematic differentiation between triage dose estimates associated with high and low dose rate (LDR) exposures, even though it is likely that after a nuclear detonation or radiologic disaster, many surviving casualties would have received a significant portion of their total exposure from fallout (LDR exposure) rather than from the initial nuclear detonation or criticality event (high dose rate exposure). This commentary discusses the issues surrounding the use of emesis as a screening diagnostic for radiation dose after LDR exposure. As part of this discussion, previously published clinical data on emesis after LDR total body irradiation (TBI) is statistically re-analyzed as an illustration of the complexity of the issue and confounding factors. This previously published data includes 107 patients who underwent TBI up to 10.5 Gy in a single fraction delivered over several hours at 0.02 to 0.04 Gy/min. Estimates based on these data for the sensitivity of emesis as a screening diagnostic for low dose rate radiation exposure range from 57.1% to 76.6%, and the estimates for specificity range from 87.5% to 99.4%. Though the original data contain multiple confounding factors, the evidence regarding sensitivity suggests that emesis appears to be quite poor as a medical screening diagnostic for LDR exposures.

INTRODUCTION

Current protocols for the medical management of radiation casualties include time-to-emesis (TE) as a way to estimate clinical dose in victims of radiation disasters in order to identify those that are at high risk for developing acute radiation syndrome (ARS). (Gusev et al.

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2001, Goans and Waselenko 2005, Flynn and Goans 2006, Demidenko et al. 2009, Mickelson 2012, AFRRI 2013, REMM 2013) Reviews of data from radiation accidents have shown a general trend between shorter onset of emesis and exposures to a higher dose, and mathematic modeling has been applied to radiation accident data to validate TE as a preliminary indicator of radiation dose in the triage setting.(Goans and Waselenko 2005, Parker and Parker 2007, Demidenko et al. 2009) These models, however, are imprecise and can lead to a high false positive rate.(Demidenko et al. 2009) Additionally, unknown dose rate, uncertain initial dose exposure information, and lack of documentation of alternative causes of emesis (e.g., anxiety, trauma, disorientation, pregnancy, and smoke or chemical exposures) commonly associated with victims of radiation accidents are all potential confounding factors for using TE as a biodosimeter.

Differences in dose rate, in particular, may lead to inaccurate triage using TE. There is substantial radiobiologic evidence indicating significant differences in normal tissue toxicity thresholds and response for low dose rate radiation as compared to high dose rate radiation. (Hall 1972, Barendsen 1982, Gordon Steel et al. 1986, Gordon Steel et al. 1987) Therefore, it might be expected that the emetic response to radiation might also be significantly different for low dose rate and high dose rate exposures. It also is well known that individuals with the same stimulus can have marked variation in their susceptibility to vomit.

The complexity of interpreting 'time' to emesis in the context of total radiation dose delivered over an extended period of time presents another problem with using TE to estimate low dose rate exposures. For high dose rate exposures, there is the assumption that a nearly instantaneous dose is delivered followed by no further radiation. Radiation dose is then estimated based on the length of time after the initial exposure to the first development of emesis. However, with low dose rate exposures, the TE scale may be on the same order as the time scale necessary to deliver a threshold dose of radiation (e.g., two Gy are delivered over a two to four hour period) resulting in uncertain utility of the TE diagnostic.

In order to better understand the effects of low dose rate exposure on the emetic response as well as to identify potential confounding factors, the clinical radiation therapy literature was examined for evidence of emesis in the context of known exposures at low rates. A publication in 1987 by Westbrook and colleagues met these criteria, using low rates of exposure in the context of total body irradiation (TBI) to suppress bone marrow and reporting onset of emesis (if any).(Westbrook et al. 1987) Though this manuscript was published over 25 years ago, it is of interest because it used therapeutic regimens to deliver relatively high total body radiation doses at low rates continuously across several hours (thus simulating fallout exposures, though that was not the original intention). In particular Westbrook et al. used outdated cobalt teletherapy machines to deliver TBI at comparably low dose rates of approximately 0.02 Gy/min (1.2 Gy/hr) and included patients that were treated in an era during which much higher doses of TBI (>8 Gy) were used for bone marrow suppression than current protocols.

Though the Westbrook et al. paper does report on interesting data derived under unique circumstances, there are many confounding factors that preclude the derivation of any firm

conclusions regarding time to emesis and estimating total dose in the context of low dose rates. Yet, it is still worthwhile to examine as part of a larger commentary on the utility of emesis as a screening diagnostic for low dose rate radiation exposures.

DATA

In the re-examination of Westbrook et al.'s paper reported here, all data were reconstructed from the initial publication. As reported by Westbrook, all patients were treated in a controlled medical environment. All patients fasted for 12 hours, were given IV fluids and received chemotherapy (either cyclophosphamide 1.8 G/m² or melphalan 110 mg/m²) prior to TBI. Westbrook notes that patients received anti-emetics only as required without any special preparation for the first 117 patients treated (out of 305 total patients). A standard sedation regimen was then given to patients treated subsequently. For the current re-analysis, only the later 107 single cobalt source patients who all received the standard sedation regimen were included, in order to eliminate the additional confounding factor of arbitrary, non-standardized administration of anti-emetics. Patients were radiated at a constant dose rate to a target dose between 9.5 Gy to 10.5 Gy of cumulative exposure in a single treatment. Based on the published data, it is known how many total patients vomited and the cumulative dose at which each patient vomited for the first time (rounded to the nearest 1 Gy – see Table 1).(Westbrook et al. 1987)

METHODS

The objective of the analysis was to attempt to determine estimates for sensitivity and specificity for emesis as a screening diagnostic using various cut points of cumulative exposure, each of which had been delivered at a constant but low dose rate. Cutoff points of 2, 3, 4, and 5 Gy were chosen for comparison. A bivariate fixed effects and mixed effects analysis of sensitivity and specificity were implemented, in order to estimate those quantities. This application of a generalized linear mixed model has been utilized previously for a meta-analysis of lymphangiography using PROC GLIMMIX in SAS 9.3.(Menke 2010) Sensitivity and specificity are modeled jointly as binomial data. More specific details of this model can be found in the method publication.(Menke 2010) Estimates of sensitivity and specificity for both the fixed effects model and the mixed effects model are reported.

RESULTS

In the fixed effect model, which does not allow random effects for subjects, estimates for sensitivity ranged from 56.3% to 69.4% for different dose cut points, while the estimates for specificity ranged from 82.2% to 99.1% (Table 2). Allowing for random effects in the model improved sensitivity and specificity estimates, where the estimates for sensitivity ranged from 57.1% to 76.6%, and the estimates for specificity ranged from 87.5% to 99.4% (Table 3). Thus, correlation within subject yielded higher sensitivity and specificity. A logistic regression model resulted in an odds ratio of 1.56 (95% CI: 1.46 to 1.68), which indicates that the odds of emesis increase 0.56 times for each 1-Gy increase of the dose .

DISCUSSION

In the event of a mass casualty scenario involving radiation exposure, casualties who received a total body radiation dose between 2 and 10 Gy are likely to benefit from advanced medical intervention.(Goans and Waselenko 2005, Hall and Giaccia 2006) In the context of many thousands (or hundreds of thousands) of people being potentially identified as victims, it is imperative to quickly assess who needs to be evaluated and treated for acute radiation syndrome (ARS) and who does not. Early identification of these victims as they exit the radiation control area, using a field-applicable screening test, is needed to appropriately identify and triage each casualty to further diagnostic study and the appropriate level of care. As discussed below, a large-scale radiation disaster provides an unusual context for evaluating the sensitivity and specificity of the test. It is especially important that people not be falsely identified as not having risk of ARS because they will have a significantly higher likelihood of dying if treatment is not provided in time.

Typically a medical screening test is an inexpensive, quick, and convenient test used to identify potential patients with a given disease and direct them to additional, more sophisticated confirmatory testing. Ideally, any medical test would have both high sensitivity and high specificity, however, in reality there are usually trade-offs between these two characteristics. Generally, it is more important that an initial screening test maximize the number of true positives so that the fewest patients with the actual disease are missed, corresponding to a high sensitivity. Additional, confirmatory testing should then have a high specificity to correctly identify those patients without the disease (true negatives).(Wilson and Jungner 1968)

In a mass casualty radiation scenario, the disease tested is radiation exposure to a threshold dose of total body radiation. All persons in the immediate area of the event are at risk for the radiation exposure. Upon screening, each person will be directed to the next level of medical evaluation or dismissed from immediate entry into the medical care system. Approximately 50% of people exposed to greater than 3.5 Gy will die within 60 days if left untreated ($LD_{50/60}$ is 3.5 Gy for TBI).(Goans and Waselenko 2005) If directed to medical care, initial diagnostics to determine dose received and a plan of care begins with lymphocyte depletion kinetics. Supportive care, such as fluid support and antibiotics, greatly reduces the chance of death in patients with radiation exposures less than 6 Gy, and advanced medical care, including colony stimulating factor (CSF) and bone marrow transplant (BMT), can save the lives of patients exposed to higher doses.(Gusev et al. 2001, Goans and Waselenko 2005, Flynn and Goans 2006, Mickelson 2012, AFRI 2013, REMM 2013)

Previous studies of the relationship of TE and dose using a common database of 108 radiation accident exposures, mostly from Chernobyl (1986), have been published.(Goans and Waselenko 2005, Parker and Parker 2007, Demidenko et al. 2009) These data all evaluate TE measured from a single time (T_0) of near instantaneous exposure. One group analyzing this accident database used a cut point of 2 Gy and found the sensitivity and specificity of emesis at 1.5 hours from T_0 to be 55% and 93%, respectively.(Demidenko et al. 2009)

There is also data from radiation experiments performed from 1964–1975 for the National Aeronautic and Space Administration (NASA) at Oak Ridge Associated Universities (ORAU) that has been used to generate informational graphics and guidelines for medical management in the event of a radiation mass casualty.(Goans and Waselenko 2005, Flynn and Goans 2006) The single exposure, high dose rate experiments showed an emesis ED₅₀ (the amount of radiation needed to cause effect in 50% of the people exposed) of 2.40 Gy, a value significantly lower than the median dose to emesis of 6 Gy delivered at a low dose rate from the Westbrook et al data.(Westbrook et al. 1987)

As mentioned previously, there are many limitations and confounding factors to the analysis presented in this commentary including the use of two different chemotherapy regimens and lack of patient-level data. One important point to note, however, is that patients were queried regarding their general anxiety level and exposure to other emetic stimuli, e.g. car travel in the original publication.(Westbrook et al. 1987) While not enough data were available to statistically analyze the correlation of these factors with emesis, vomiting was noted to occur more frequently in those who self-identified as being prone to vomit in general and those individuals with higher general anxiety levels. This observation from the original paper would seem to be especially relevant in the scenario of a nuclear disaster given that there would likely be significantly elevated anxiety levels.

Though significant confounding factors are present, an analysis of the occurrence of emesis at any time during a constant low dose rate exposure up to approximately 10 Gy over a period of approximately 8–9 hours was performed for the purpose of illustrating the significant differences between emesis in high dose rate and low dose rate exposures. However, the data only indirectly yielded time-to-emesis (TE) as the time value was derived from the delivered dose and the dose rate of 0.02 Gy/min. It is recognized that most current emergency response recommendations are based on time-to-emesis. However, with a low dose rate exposure like the current study, the time necessary to deliver a threshold radiation dose is on the same order as the traditional TE threshold values. As a result of this fact, in the current study, emesis was treated as a simple binary variable for the purposes of calculating a rudimentary sensitivity and specificity. Of note, this approach is similar to the textbook presentations of the NASA data from ORAU.(Goans and Waselenko 2005, Flynn and Goans 2006)

It should also be noted that current military recommendations from the Armed Forces Radiobiology Research Institute (AFRRI) indicate both percent of an exposed population with emesis (% emesis) and TE for exposed individuals are useful diagnostic tools indicating radiation exposure.(AFRRI 2013) The current study has generally lower % emesis at each dose level compared to the current military guidelines which are based on nearly instantaneous, high dose rate exposures (e.g. . 39.3% in the current study versus 72% at 4 Gy). (AFRRI 2013) This is consistent with known radiobiologic principles that indicate increased threshold doses for acute toxicity with lower dose rate radiation exposure. (Hall 1972, Barendsen 1982, Gordon Steel et al. 1986, Gordon Steel et al. 1987, Brenner and Hall 1991)

Although the data presented in this commentary do not have a time component to the sensitivity analysis and includes confounding clinical factors, the analysis still offers important insights into the utility of emesis as a medical screening diagnostic for low dose rate exposures. If the sensitivity of emesis when analyzed as a simple diagnostic binary variable in a standardized clinical environment is quite poor, it might be expected that any number of additional environmental or situational emetic stimuli (in the case of a nuclear disaster) would only worsen its reliability.

The current illustrative statistical example derived from Westbrook et al., to the best of the authors' knowledge, is the only such published analysis evaluating the sensitivity and specificity of emesis as a diagnostic for low dose rate radiation exposure in humans with the dose delivered by known clinical methods at the time of treatment. Though emesis is an inexpensive, quick, and convenient test available in the field for initial screening, a low sensitivity, median dose to emesis higher than the LD_{50/60} for TBI, and the severe consequence of a missed diagnosis indicate that emesis is likely to be a poor screening test for low dose rate radiation exposure in a mass casualty scenario. Currently, no other field tests are officially recommended for radiation screening at the radiologic control area (the assessment, triage, and decontamination area that all people at the site of a radiation mass casualty must pass through to exit the area). After the initial assessment, lymphocyte kinetics are used to estimate TBI dose, but this test requires at least 18 hours to obtain initial results and would be difficult to implement on a large scale. (Parker and Parker 2007) Thus, this commentary and the associated illustrative analysis underscores the need for a quick, readily available field dosimeter with high sensitivity at 2 Gy to enhance the ability to appropriately triage victims of a radiation mass casualty event.

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Table 1

Number of patients who experience emesis for the first time at each dose, and the cumulative number of patients who experience emesis at each dose. 27 out of 107 patients never experience emesis.

Dose (Gy)	Experience Emesis (1 st time)	Cumulative total
0	0	0
1	1	1
2	1	2
3	18	20
4	20	40
5	11	51
6	11	62
7	10	72
8	5	77
9	3	80
10	0	80

Table 2

Fixed effects estimates and 95% confidence intervals for sensitivity and specificity for dose cut points at 2, 3, 4, and 5 Gy.

Dose Cut Point (Gy)		Pooled Sensitivity	Pooled Specificity
High Dose > 2, Low Dose	2	56.3% (52.9, 59.6)	99.1% (97.1, 99.7)
High Dose > 3, Low Dose	3	61.7% (58.1, 65.1)	94.6% (92.0, 96.4)
High Dose > 4, Low Dose	4	65.7% (62.0, 69.3)	88.2% (85.2, 90.7)
High Dose > 5, Low Dose	5	69.4% (65.3, 73.1)	82.2% (79.1, 85.0)

Table 3

Mixed effects estimates and 95% confidence intervals for sensitivity and specificity for dose cut points at 2, 3, 4, and 5 Gy.

Dose Cut Point (Gy)		Pooled Sensitivity	Pooled Specificity
High Dose > 2, Low Dose	2	57.1% (46.2, 67.3)	99.4% (97.6, 99.9)
High Dose > 3, Low Dose	3	66.4% (55.9, 75.5)	96.4% (93.4, 98.1)
High Dose > 4, Low Dose	4	72.0% (62.4, 79.9)	91.8% (87.3, 94.8)
High Dose > 5, Low Dose	5	76.6% (67.6, 83.7)	87.5% (81.7, 91.6)