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Multifactorial analysis on the short-term side effects occurring within 96 hours after radioiodine-131 therapy for differentiated thyroid carcinoma

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Objective: This study was performed to clarify factors that might influence short-term side effects occurring within 96 hours after administration of ^{131}I for patients with thyroid carcinoma. ***Methods:*** In 71 patients with differentiated thyroid carcinoma, short-term side effects including gastrointestinal complaints, salivary gland swelling with pain, change in taste and headache were retrospectively analyzed. All patients were given domperidone for prevention of gastrointestinal complaints and advised to consume sour foods to promote discharge of radioiodine from the salivary glands. Selected factors possibly affecting the incidence of side effects were dose per body weight, TSH, effective half-life of ^{131}I, sex, age, ^{131}I accumulation into the stomach and salivary glands, and edema prior to radioiodine administration. The factors were evaluated by multivariate analyses. ***Results:*** Incidence of gastrointestinal complaints, salivary gland swelling with pain, change in taste and headache was 65.2%, 50.0%, 9.8% and 4.4%, respectively. In gastrointestinal complaints, the incidence of appetite loss, nausea and vomiting was 60.9%, 40.2% and 7.6%, respectively. The gastrointestinal complaints increased significantly in the patients dosed above 55.5 MBq/kg and with TSH elevation. For salivary gland swelling with pain, female patients displayed a significantly higher incidence than males. No statistically significant factors were detected for change in taste or headache. ***Conclusions:*** Significant factors influencing short-term side effects were dose per body weight and TSH values for gastrointestinal complaints, and female sex for salivary gland swelling with pain. Our preliminary experience suggests that the most frequent gastrointestinal complaints can be prevented with ramosetron.

Key words: radioiodine therapy, thyroid cancer, short-term side effects, dose, TSH

INTRODUCTION

RADIOIODINE-131 therapy for differentiated thyroid carcinoma is known to be associated with several side effects.[1–3] There are reports concerning intermediate (from discharge up to 3 months) and long-term (greater than 3 months after treatment) side effects.[4–8] However, only limited reports are available regarding short-term side effects occurring within 96 hours following ^{131}I administration and resolving completely within ten days.[1,2] This study was performed to clarify factors that might affect the short-term side effects.

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MATERIALS AND METHODS

Patients

From January 1998 to December 2000, 71 patients underwent radioiodine therapy for differentiated thyroid carcinoma in our hospital. Short-term side effects were examined retrospectively via review of nursing charts and charts of attending physicians. The patient's age at the time of radioiodine treatment was 50 ± 15 years (mean ± standard deviation, range 17–74 years). The sample

population comprised 46 females and 25 males. Sixty-five patients had papillary carcinoma and six patients follicular carcinoma. Total thyroidectomy with neck dissection was performed in all patients prior to radioiodine therapy. At the time of total thyroidectomy, 43 patients had only cervical lymph node metastases; 28 patients had distant metastases such as lung, bone and brain metastases. Fifty patients were given single treatments and 21 patients double treatments. In total, 92 treatments were performed. Sixty treatments with 3,885 MBq ^{131}I were given for patients only with local metastases. Thirteen treatments with 5,735 MBq ^{131}I and 19 treatments with 7,585 MBq ^{131}I were given for patients with distant metastases.

Protocol

All patients were withdrawn from levothyroxine 6 weeks prior to admission for radioiodine therapy. Substitution of triiodothyronine was initiated after withdrawal of levothyroxine and was continued until 2 weeks before admission. A low iodine diet was initiated 2 weeks prior to admission and was discontinued upon release from the isolation room. To prevent hypothyroidism, triiodothyronine was initiated within 24 hours before and after the radioiodine administration.

To prevent gastrointestinal side effects, all patients received 10 mg domperidone per dose with 3 doses per day for three days beginning from the morning of radioiodine administration. To promote discharge of radioiodine from the salivary glands, all patients were advised to consume sour foods such as pickled Japanese apricots, pickled scallions and lemon candies.

TSH values were always measured within five days before radioiodine administration.

Short-term side effects

Four kinds of short-term side effect were observed in this investigation: gastrointestinal complaints, salivary gland swelling with pain, change in taste and headache. Appetite loss, nausea and vomiting were included in gastrointestinal complaints. Appetite loss was observed before radioiodine administration in 10 treatments, and seemed to be due to hypothyroidism. They were excluded from the cases of gastrointestinal complaints in the study.

Risk factors

Dose per body weight, and effective half-life were selected as factors affecting whole-body dosimetry, which is closely related to the occurrence of side effects. TSH levels and presence of edema of face and extremities were chosen to judge whether the degree of hypothyroidism could affect the incidence of side effects. The tracer accumulation into the stomach and salivary glands was selected as the factor related to injuries to the gastric mucosa and salivary glands.

The relationship between dose per body weight and

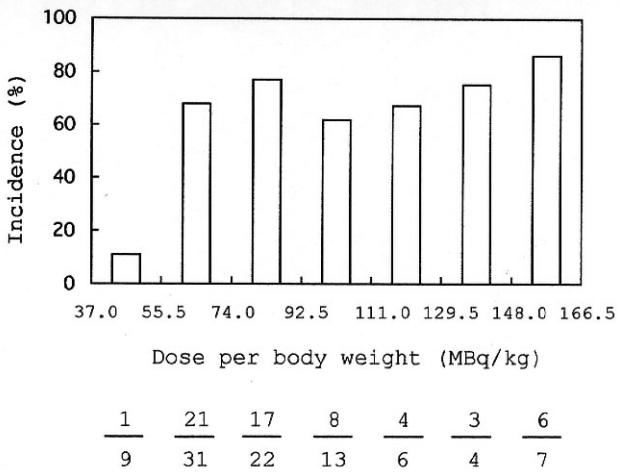

Fig. 1 Effect of dose per body weight on incidence of gastrointestinal complaints. Numerators represent the number of cases displaying gastrointestinal complaints and denominators represent the number of whole cases for every interval of 18.5 MBq/kg.

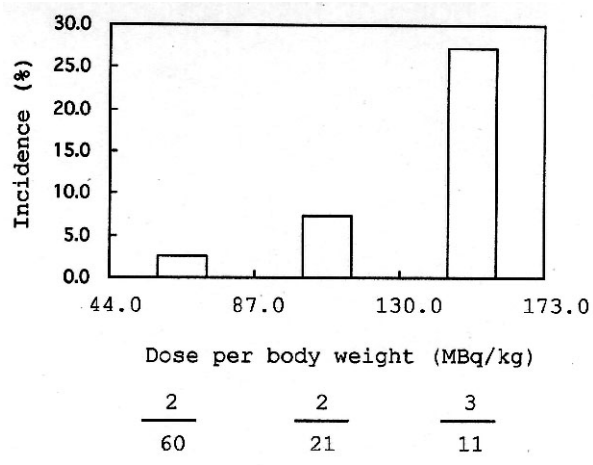

Fig. 2 Effect of dose per body weight on incidence of vomiting. Numerators represent the number of cases displaying gastrointestinal complaints and denominators represent the number of whole cases for every interval of 43.0 MBq/kg.

side effects was assessed for every 18.5 MBq per kg interval. Additionally, side effects were evaluated for every ten-year of age interval.

Evaluation of uptake and effective half-life of radioiodine

On the third and seventh days following oral administration of radioiodine, whole-body images were scanned utilizing a large field of view gamma camera (GCA-901A/w2, Toshiba, Tokyo, Japan) equipped with high-resolution, parallel hole collimators for each patient. The third day images were employed for visual evaluation of uptake in the stomach and salivary glands. Whole-body radioactivity was routinely measured at 0, 1, 2, 3, 4 and 7 days after oral administration of radioiodine, and then the

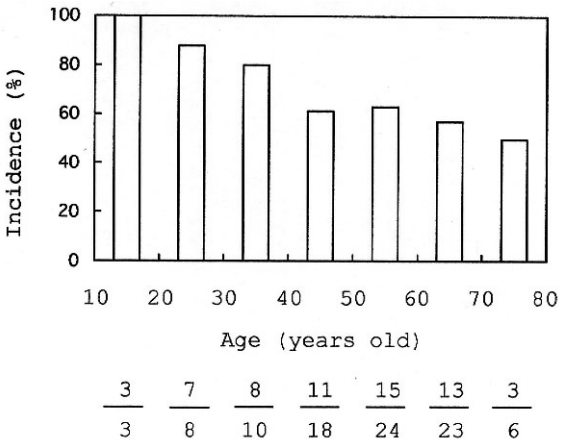

Fig. 3 Effect of patient age on incidence of gastrointestinal complaints. Numerators represent the number of cases displaying gastrointestinal complaints and denominators represent the number of whole cases for every ten-year of age interval.

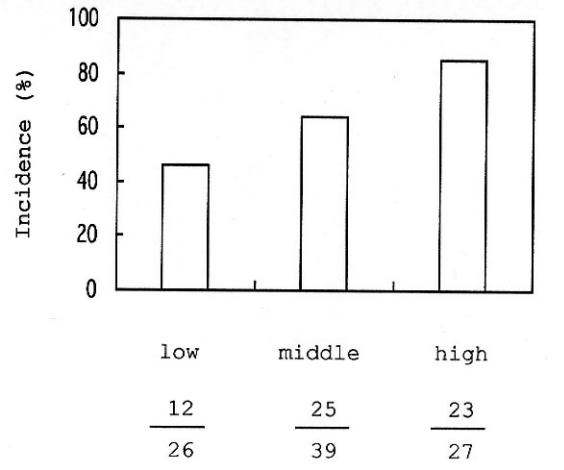

Fig. 4 Effect of TSH on incidence of gastrointestinal complaints. Numerators represent the number of cases displaying gastrointestinal complaints and denominators represent the number of whole cases for three groups with low (TSH < 90 μU/m*l*), middle (90 ≤ TSH < 180) and high (180 ≤ TSH) values.

effective half-life was estimated by linear regression analysis on a semi-logarithmic scale.

Statistical analysis

Statistical analysis was conducted using StatView-J5.0 PC software (SAS, NC, USA) for multivariate analyses and Statcel97 PC software (OMS, Saitama, Japan) for the Spearman's correlation coefficient by rank test, Fisher exact p tests and a simple linear regression analysis. All percentage values are expressed as one decimal place. A multivariate analysis was performed with a stepwise logistic regression model. When variables with p values larger than 0.05 were encountered following the first step of multivariate analysis, the variable with the greatest p value was removed from the model. The subsequent step of multivariate analysis with remaining variables was continued until all remaining variables exhibited p values below 0.05. Data are expressed as odds ratio with 95% confidence intervals. The Spearman's correlation coefficient by rank test, Fisher exact p tests and a simple linear regression analysis were performed when appropriate. Statistical significance was set at $p < 0.05$.

Table 1-A Multivariate analysis for gastrointestinal complaints

Factor	Odds ratio	P value	95% confidence interval
Dose per body weight*	0.068	0.0247	0.007–0.710
TSH†	1.010	0.0191	1.002–1.018
Age‡	0.959	0.0496	0.919–1.000
Effective half-life†	1.148	0.1908	0.933–1.413
Female§	1.464	0.5134	0.466–4.597
Uptake in stomach¶	2.027	0.3133	0.513–8.004
Edema#	0.740	0.5891	0.248–2.209

* Dose per body weight: < 55.5 MBq/kg versus ≥ 55.5 MBq/kg
† Continuous variable
‡ Age stratified by one-year increment
§ Versus male
¶ Uptake in stomach: negative versus positive
# Edema: absent versus present

Table 1-B Multivariate analysis for vomiting

Factor	Odds ratio	P value	95% confidence interval
Dose per body weight*	0.137	0.0692	0.016–1.169
TSH†	1.006	0.1411	0.998–1.015
Age‡	0.971	0.3987	0.907–1.040
Effective half-life†	1.107	0.5491	0.794–1.544
Female§	13.11	0.1439	0.415–413.6
Uptake in stomach¶	0.010	0.9957	0.011–990.9
Edema#	1.257	0.8200	0.175–9.018

* Dose per body weight: < 130.0 MBq/kg versus ≥ 130.0 MBq/kg
† Continuous variable
‡ Age stratified by one-year increment
§ Versus male
¶ Uptake in stomach: negative versus positive
# Edema: absent versus present

RESULTS

Gastrointestinal complaints, salivary gland swelling with pain, change in taste and headache occurred in 60 (65.2%), 46 (50.0%), 9 (9.8%) and 4 patients (4.4%), respectively. In gastrointestinal complaints, appetite loss, nausea and vomiting occurred in 56 (60.9%), 37 (40.2%) and 7 patients (7.6%), respectively.

The incidence of gastrointestinal complaints increased significantly from 11.1% to more than 60.0% in the patients dosed above 55.5 MBq/kg (Fig.1, Fisher exact p test, $p < 0.001$). Vomiting, a clear and severe sign among gastrointestinal complaints, also increased significantly

Table 2 Multivariate analysis for salivary gland swelling with pain

Factor	Odds ratio	P value	95% confidence interval
Dose per body weight*	1.009	0.2509	0.993–1.026
TSH*	1.000	0.9776	0.996–1.004
Age†	0.992	0.6224	0.961–1.024
Effective half-life*	0.983	0.7706	0.878–1.102
Female‡	3.950	0.0062	1.476–10.57
Uptake in salivary glands‖	1.183	0.8384	0.234–5.974
Edema¶	0.986	0.9776	0.376–2.587

* Continuous variable
† Age stratified by one-year increment
‡ Versus male
‖ Uptake in salivary glands: negative versus positive
¶ Edema: absent versus present

Table 3 Multivariate analysis for change in taste

Factor	Odds ratio	P value	95% confidence interval
Dose per body weight*	1.018	0.1140	0.996–1.042
TSH*	1.002	0.4442	0.997–1.007
Age†	0.986	0.6055	0.935–1.040
Effective half-life*	0.949	0.6588	0.752–1.197
Female‡	0.733	0.7135	0.140–3.845
Uptake in salivary glands‖	0.724	0.7886	0.068–7.686
Edema¶	0.861	0.8561	0.170–4.350

* Continuous variable
† Age stratified by one-year increment
‡ Versus male
‖ Uptake in salivary glands: positive versus negative
¶ Edema: absent versus present

Table 4 Multivariate analysis for headache

Factor	Odds ratio	P value	95% confidence interval
Dose per body weight*	1.017	0.3390	0.983–1.052
TSH*	0.997	0.4773	0.987–1.006
Age†	0.947	0.1955	0.871–1.029
Effective half-life*	1.005	0.9668	0.788–1.281
Female‡	0.522	0.5667	0.057–4.825
Edema‖	0.627	0.7132	0.052–7.578

* Continuous variable
† Age stratified by one-year increment
‡ Versus male
‖ Edema: absent versus present

from below 10.0% to 27.3% in the patients dosed above 130.0 MBq/kg (Fig. 2, Fisher exact p test, $p < 0.05$). Based on these results, doses per weight were treated as categorical data for gastrointestinal complaints in the multivariate analysis. Additionally, gastrointestinal complaints decreased with age and increased with TSH elevation (Figs. 3 and 4).

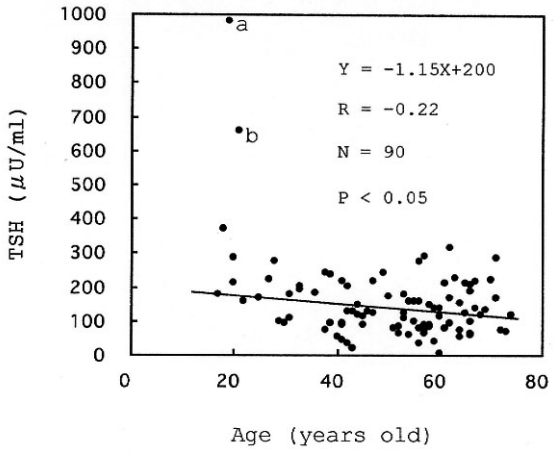

Fig. 5 Correlation between age and TSH.

In the first step of multivariate analysis for gastrointestinal complaints, dose per body weight, TSH and age were shown as significant (Table 1-A). Following the process involving deletion of statistically less significant factors, dose per body weight remained significant with an odds ratio of 0.052 (group receiving < 55.5 MBq/kg versus group receiving ≥ 55.5 MBq/kg, p = 0.0099, 95% confidence interval between 0.006 and 0.492); furthermore, TSH remained a secondly significant factor with an odds ratio of 1.009 (p = 0.0170, 95% confidence interval between 1.002 and 1.016).

The first step of multivariate analysis for vomiting indicated no significant factors (Table 1-B). However, after deletion of statistically less significant factors, dose per body weight remained significant with an odds ratio of 0.122 (group receiving < 130.0 MBq/kg versus group receiving ≥ 130.0 MBq/kg, p = 0.0305, 95% confidence interval between 0.018 and 0.820); furthermore, TSH remained a secondly significant factor with an odds ratio of 1.007 (p = 0.0308, 95% confidence interval between 1.001 and 1.013).

Unlike gastrointestinal complaints, doses per body weight, age and TSH had no significant relationships with the incidences of the other kinds of side effects (Figures not shown).

Only female sex was shown as significant in the first step of multivariate analysis for salivary gland swelling with pain (Table 2), and remained significant after deletion of less significant factors with an odds ratio of 4.286 (female versus male, p = 0.0017, 95% confidence interval between 1.726 and 10.64).

No significant factors were indicated in the first step of multivariate analyses for change in taste or headache (Tables 3 and 4), and no factors remained significant in the final step of multivariate analyses for either change in taste or headache.

DISCUSSION

Knowledge of the predictors of side effects will facilitate administration of better preventive medications for patients treated with radioiodine. Despite the administration of domperidone in the study, gastrointestinal complaints were most frequently observed. The incidence was almost the same as in a study in which no medication was used by Nostrand et al.[1] (65.2% versus 66.7%). Based on the results, we changed domperidone to ramosetron hydrochloride in September 2002. Subsequently, no patients have experienced severe gastrointestinal complaints such as vomiting. As antiemetics, the targets of domperidone and ramosetron are different, with the former working on the chemoreceptor trigger zone in the fourth ventricle and the latter on the abdominal afferent vagus nerve. The effectiveness of ramosetron suggested that the vomiting was derived from the stimuli toward the abdominal afferent vagus nerve in acute radiation gastritis.

Age was a significant factor in the first step of multivariate analysis for gastrointestinal complaints, but became insignificant through the process of deleting less significant factors. As dependence of TSH value on age was suspected, the correlation between the two factors was analyzed (Fig. 5). There was a weak, but not significant correlation between them (Spearman's correlation coefficient by rank test, $r = -0.1972$, $p = 0.0594$). After excluding the two data points with exceptionally large TSH values (points a and b in Fig. 5), a simple linear regression analysis was performed. There was a significant linear relationship between TSH value and age (continuous line in Fig. 5).

It is supposed that patients with severe hypothyroidism are more susceptible to side effects. The speculation was verified with the multivariate analysis that showed the significance of TSH values in the incidence of gastrointestinal complaints. TSH values also significantly affected the incidence of vomiting. It seems that TSH itself causes vomiting since the use of recombinant human TSH is reported to have the side effects of vomiting and nausea.[9,10] No significant difference was found in the incidence of side effects between the patients with and without edema. Presence of edema is a qualitative factor and inappropriate for precise evaluation of the degree of hypothyroidism.

Gastrointestinal complaints and salivary gland swelling with pain are believed to be associated with radiation gastritis and sialoadenitis. Therefore, we suspected that the uptake in the stomach and salivary glands was an indicator of the side effects, although no significance was found. The eye ball evaluation of the tracer uptake on the third day scan did not reflect the absorbed doses of the organs that seemed to be more appropriate for the analysis.

Female patients' susceptibility to salivary gland swelling with pain was shown. The reason is not clear, but one possibility is a difference in the psychological response to radiation therapy between the sexes.

The incidence of headache was extremely low; therefore, headache could be a non-specific symptom that depends on the sensitivity to stress and anxiety associated with isolation.

CONCLUSIONS

It was clarified that significant factors influencing short-term side effects were dose per body weight and TSH values for gastrointestinal complaints, and female sex for salivary gland swelling with pain. Gastrointestinal complaints occur most frequently, and our preliminary experience suggests that an appropriate medication such as ramosetron can prevent them.

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