Radioiodine pharmacokinetics in Grave’s Disease and Nodular Toxic Goiter. Simplified calculation of therapeutic activity

A A Trukhin$^{1,2}$, PO Rumyantsev$^1$, Ya I Sirota$^1$, V S Yasuchenya$^1$, K Yu Slaschuk$^1$, M S Sheremeta$^1$, M V Degtyarev$^1$, V G Nikitaev$^2$, A N Pronichev$^2$

E. V. Polyakov$^2$

$^1$Endocrinology research center, str. Dmitry Ulyanov 11, 117036, Moscow, Russia.
$^2$National Research Nuclear University MEPhI (Moscow Engineering Physics Institute), Kashirskoe shosse 31, 115409, Moscow, Russia.
E-mail: alexey.trukhin12@gmail.com

Abstract. Existing European standard recommendations for dosimetry examination in case of thyrotoxicosis offers difficult to repeat examination protocols. The individual pharmacokinetics data of 343 patients diagnosed with Graves and Plummer disease and 133 cases with known thyroid volume are presented in the article. The data underwent parametrical statistical analysis. As a result, two clinically reproducible methods of calculating therapeutic activity have been proposed.

1. Introduction
In the last 5 years an increase in evidence of the radioiodine therapy effectiveness in the case of dosimetry based calculated observed. The standard activities method shows 61% efficiency [1,7].

EANM recommendations suggest 4 ways of therapeutic activity calculating. The first guide to collect more than 3 measurements with the further fitting of experimental data to obtain thyroid functional parameters. The second method suggests to obtain two measurements: the first for 1-4 days, the second for 4-8 days. The measurement interval must be at least 3 days. According to recommendations, measured activities are used to find the biological half-life of iodine excretion from the thyroid gland and if it exceed 8 days then effective half-life should be considered as 8 days. Such simplification leads to higher therapeutic activity misestimating and higher absorbed dose to the whole body [5,6]. The third way tells about a good correlation of the radioiodine uptake on 4-8 day with cumulated activity. The fourth method suggests taking one measurement in 1 to 4 days gap and then using a standard effective half-life time of iodine $T_{eff} = 5.5$ hours calculate therapeutic activity of 131-iodine [2].

The implementation of the method consists of equipment calibration, pharmacokinetic data collection, volume of thyroid tissue measurement, therapeutic activity calculation, according to prescribed dosimetry parameter by the radiologist [3,4,8].

This article presents an analysis of 131-iodine pharmacokinetics data for a 48-hour period after oral administration and methods for therapeutic activity calculation.
2. Materials and methods
The implemented in practice dosimetry planning protocol of radioiodine therapy starts from administering of 5-10 MBq 131-iodine tracer activity. Activity measure take at 1-2 hours, 5-7 hours, 23-25 hours, 47-49 hours (in contrast to EANM protocol: 4-6 hours, 24-48 hours, 120-196 hours) using a GE single-photon emission computer tomography NM 630 system or NM / CT 670. The ratio of gamma quanta registered within the 15% energy window of 364.5 keV to the administered activity per second K is determined within the configuration of the equipment: scintillator thickness, HEGP collimators, uniformity, gamma-camera graduated to $^{99m}$Tc, fixed temperature 21-23 °C:

$$K = -0.35 \ast m + 95, \frac{counts/s}{kBq}$$ (1)

where m is the patient's body weight.

To determine the left and right lobe of the thyroid gland volumes ($V_L$ [cm$^3$], $V_R$ [cm$^3$]) from the measured longitudinal y [cm] and transverse x [cm] dimensions the next equations was used:

$$V_L = 0.48 \ast x \ast y \ast (x - 0.3), [cm^3]$$ (2)

$$V_R = 0.48 \ast x \ast y \ast (x - 0.3), [cm^3]$$ (3)

Collected data archived in DICOM files. For image processing Matlab developed script was used. To determine pixels belonged to thyroid was used Table 1 of thresholds (thyroid tissue is located in the center of the scintigraphic image).

| Time of measurements after administration, h | Threshold |
|--------------------------------------------|-----------|
| 1-2                                       | 0.66      |
| 5-7                                       | 0.86      |
| 23-25                                     | 0.86      |
| 47-49                                     | 0.86      |

The lower limit of dosimetry planning cases acceptance in study corresponds to the upper limit of normal uptake of 131-iodine activity (25%). 231 patients with diagnosed diffuse toxic goiter, 112 patients with diagnosed nodal toxic goiter; among them 133 patients with confirmed thyroid volume.

The data pre-processing consisted of volume and uptakes logarithmization in order to transform the real lognormal distribution to the usual normal distribution. The Pearson's agreement criterion and the Student's t-test was applied.

3. Results and discussions
The observed samples of the logarithmized of thyroid volumes at the observed maximum at 5-7 hours (69 patients) and 23-25 hours (74 patients) correspond to the normal distribution law ($\alpha = 0.01$, $p = 0.28$) and ($\alpha = 0.01$, $p = 0.86$), respectively. Samples are obtained from different sampling frames populations and have a normal distribution with different mean values ($\alpha = 0.01$, $p = 0.0000007$).

The above analysis of the data determines two groups of the logarithmized values of thyroid volumes at the observed accumulation maximum as groups obtained from different general sampling frames:

1) 5-7 hours (Mean of the general sample = 43 ± 2 ml)
2) 23-25 hours (Mean of the general sample = 28 ± 2 ml)

The observed samples of the logarithmized values of the maximum accumulation of 131-iodine in Graves disease (231 patients) and Plummer (112 patients) correspond to the normal distribution law ($\alpha = 0.01$, $p = 0.65$) and ($\alpha = 0.01$, $p = 0.0237$), respectively. Samples are obtained from the one sample frame and have a normal distribution with the same average values ($\alpha = 0.01$, $p = 0.72$).
The above analysis of the data determines one group of the logarithmized values of the maximum accumulation of 131-iodine for Graves and Plammer as the groups obtained from one general sample frame (Mean of the general sample frame = 38 ± 1%).

The observed samples of the logarithmized effective half-lives of 131-iodine from thyroid gland less (90 patients) and more (44 patients) then 43 ml correspond to the normal distribution law (\(\alpha = 0.01, p = 0.1377\)) and (\(\alpha = 0.01, p = 0.4513\)), respectively. The above samples are obtained from the general sample frame and have a normal distribution with the same average values (\(\alpha = 0.01, p = 0.4257\)).

The data analysis resulted in the determination of the effective half-life of 131-iodine from thyroid gland in volumes less or more than 43 ml as groups obtained from one general sample frame (Mean sample mean = 156 ± 2 h).

3.1. Therapeutic activity calculation using maximum uptake measurements

According to the results of analysis, optimal time to measure maximum uptake of 131-iodine MU [%] is 5-7 h for volumes more than 41 ml and 23-25 h for volumes less than 41 ml.

\[
A_{therapeutic} = \max \left( \frac{DR}{U_L \cdot MU \cdot V_L^{-0.97} \cdot 3 \cdot 10^{-5}} \right)
\]

(4)

where DR [Gy/s] is the absorbed dose rate (prescribed by the nuclear medicine physician), \(U_L\) [%], \(U_R\) [%] - uptake distribution between lobes, \(V_L\) [ml], \(V_R\) [ml] – left and right lobe volumes.

3.2. Therapeutic activity calculation using second hour after 131-iodine administration

For the first to second hour after oral administration of 131-iodine, a static scintigraphy of the thyroid gland is performed. Determine the uptake relative to the administered activity using 66% threshold. To calculate prognosed uptake next equations are used (5, 6, 7):

\[
U_{5-7} = -2.58 \cdot U_{1-2}^2 + 1.80 \cdot U_{1-2} + 0.14
\]

(5)

\[
U_{23-25} = -1.72 \cdot U_{1-2}^2 + 0.94 \cdot U_{1-2} + 0.26
\]

(6)

\[
U_{47-49} = -0.21 \cdot U_{1-2}^2 + 0.20 \cdot U_{1-2} + 0.29
\]

(7)

Fitted uptake curves and relative error of the predicted value \(\varepsilon\) is shown on (Figure 1, Figure 2, Figure 3).
Figure 1. (Left) 5-7 h uptake dependence from 1-2 h uptake; (Right) Relative error of prognosis

Figure 2. (Left) 23-25 h uptake dependence from 1-2 h uptake; (Right) Relative error of prognosis

Figure 3. (Left) 47-49 h uptake dependence from 1-2 h uptake; (Right) Relative error of prognosis
The predicted maximum uptake MU and graphically determined $\varepsilon$ is used in the therapeutic activity calculation according to:

$$A_{therapeutic} = \max \left( \frac{DR}{U_L \cdot MU \cdot (1 - \varepsilon) \cdot V_{L}^{-0.97} \cdot 3 \cdot 10^{-5}} \right) \quad (8)$$

4. Conclusion

The paper describes dosimetry planning examination protocol beginning from fundamental research of radiiodine pharmacokinetics in Graves and Plummer diseases. The results indicate the importance of first 48 hours in dosimetry planning of radioiodine therapy. Pharmacokinetics depends on the volume of the gland. Maximum uptake time moves to the fast uptake within volume increase. There are no differences in Graves and Plummer disease pharmacokinetics. Two simplified methods are presented that might be used for urgent cases of Graves and Plummer disease, when there is no time to investigate the complete pharmacokinetic curve.

5. References

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