

**IN VIVO INTERACTION OF PROPYLTHIOURACIL WITH SODIUM IODIDE (Na<sup>131</sup>I)  
RADIOPHARMACEUTICAL IN RATS (*Rattus norvegicus*)**

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**ABSTRACT**

**IN VIVO INTERACTION OF PROPYLTHIOURACIL WITH SODIUM IODIDE (Na<sup>131</sup>I)  
RADIOPHARMACEUTICAL IN RATS (*Rattus norvegicus*).** The aim of this research is to determine the effect of propylthiouracil (PTU) treatment to pharmacokinetics interaction and biodistribution profile of Na<sup>131</sup>I radiopharmaceuticals. Three groups of animal model were used in this experiment, i.e. experimental animals which given PTU for 1 time (onset or A groups), PTU for six days (B Groups) and without treatment (control or C Groups). Pharmacokinetics and biodistribution test were conducted by giving PTU per oral and after 24 hours, continued by giving Na<sup>131</sup>I solution per oral. In pharmacokinetics test, percentage of injection dose/gram of blood (%ID/g) was calculated to determine the absorption, distribution and elimination half time. In biodistribution test, percentage of injection dose/gram of organs was calculated to determine the accumulation of Na<sup>131</sup>I in specific organs. The results showed that the absorption half time of A, B and C groups were  $3.14 \pm 1.42$ ,  $2.49 \pm 0.49$  and  $2.52 \pm 0.7$  hours, respectively. The distribution half time of A, B and C groups were  $10.58 \pm 5.85$ ,  $12.92 \pm 3.75$  and  $11.42 \pm 3.15$  hours, respectively. The elimination half time of A, B and C groups were  $113.03 \pm 46.03$ ,  $96.57 \pm 47.76$  and  $196.71 \pm 145.21$  hours, respectively. Biodistribution test results showed that the accumulation of Na<sup>131</sup>I in thyroid of A, B and C groups were  $1.31 \pm 0.45$ ,  $5.03 \pm 0.55$  and  $4.45 \pm 2.24\%$  respectively. This research was concluded that onset and long term PTU administration cannot alter absorption, distribution, and elimination half time Na<sup>131</sup>I, and administration PTU by onset can decrease accumulation of Na<sup>131</sup>I on thyroid, different with administration PTU in long term which can not alter accumulation of Na<sup>131</sup>I on thyroid.

**Keywords:** Iodine-131, propylthiouracil, in vivo interaction, pharmacokinetics, biodistribution.

**ABSTRAK**

**INTERAKSI IN VIVO PROPILTIOURASIL TERHADAP RADIOFARMAKA SODIUM IODIDA (Na<sup>131</sup>I) PADA TIKUS (*Rattus norvegicus*).** Tujuan penelitian ini untuk menentukan efek pemberian Propiltiourasil (PTU) terhadap interaksi farmakokinetik dan profil Na<sup>131</sup>I. Tiga kelompok hewan model digunakan, yaitu hewan coba yang diberi PTU 1 kali (onset atau grup A), PTU selama 6 hari (grup B), dan tanpa perlakuan (kontrol atau grup C). Uji farmakokinetik dan biodistribusi dilakukan dengan memberikan PTU secara per oral, setelah 24 jam dilanjutkan pemberian larutan Na<sup>131</sup>I secara per oral. Pada uji farmakokinetik, persentase dosis injeksi per gram darah (%ID/g) dihitung untuk menentukan waktu paruh absorpsi, distribusi dan eliminasi. Pada uji biodistribusi, persentase dosis injeksi per gram organ dihitung untuk menentukan akumulasi Na<sup>131</sup>I pada organ spesifik. Hasil penelitian menunjukkan waktu paruh absorpsi dari grup A, B dan C masing-masing  $3.14 \pm 1.42$ ,  $2.49 \pm 0.49$  dan  $2.52 \pm 0.7$  jam. Waktu paruh distribusi dari grup A, B dan C masing-masing  $10.58 \pm 5.85$ ,  $12.92 \pm 3.75$  dan  $11.42 \pm 3.15$  jam. Waktu paruh eliminasi dari grup A, B dan C masing-masing  $113.03 \pm 46.03$ ,  $96.57 \pm 47.76$  and  $196.71 \pm 145.21$  jam. Hasil uji biodistribusi menunjukkan Na<sup>131</sup>I di tiroid dari grup A, B dan C

masing-masing adalah  $1.31 \pm 0.45$ ,  $5.03 \pm 0.55$  and  $4.45 \pm 2.24\%$ . Penelitian ini menyimpulkan bawa pemberian PTU secara onset dan jangka panjang tidak mengubah absorpsi, distribusi, dan eliminasi dari  $\text{Na}^{131}\text{I}$ , namun terjadi penurunan akumulasi  $\text{Na}^{131}\text{I}$  di tiroid pada pada pemberian PTU secara onset, berbeda dengan pemberian PTU jangka panjang yang tidak merubah akumulasi  $\text{Na}^{131}\text{I}$  di tiroid.

**Kata kunci:** Iodine-131, propiltiourasil, interaksi in vivo, farmakokinetik, biodistribusi.

## 1. INTRODUCTION

Hyperthyroidism is a pathological disorder in which excess thyroid hormone is synthesized and secreted by the thyroid gland beyond the normal content range. Hyperthyroidism can be overt or subclinical. Over hyperthyroidism is characterized by low serum thyroid stimulating hormone (TSH) concentrations and raised serum concentrations of thyroid hormones: thyroxine (T4), tri-iodothyronine (T3), or both. Subclinical hyperthyroidism is characterized by low serum TSH, but normal serum T4 and T3 concentrations. The three options for treating patients with hyperthyroidism are antithyroid drugs (ATDs), radioactive iodine ablation, and surgery (1,2).

Sodium iodide ( $\text{Na}^{131}\text{I}$ ) radiopharmaceuticals usually used to therapy of hyperthyroidism in nuclear medicine. Radioiodine therapy is considered definitive therapies surgery, since the primary goal of this approach to treatment is to destroy hyperfunctioning thyroid tissue by its beta emission. Beta emission is well-known for causing death of cells because it can penetrate other cells up to several millimeters away. I-131 effectively ablating functional thyroid tissue over the course of 6 to 18 weeks or more. It is administered orally with activities of 1-5 mCi or less. Radioiodine

(I-131) use has advantages of low cost and a long half-life until 8.2 days. (3-6).

Thionamides, a class of anti thyroid drugs (ATDs), are compounds that are known to inhibit thyroid hormone synthesis via the inhibition of organification of iodine to tyrosine residues in thyroglobulin and the coupling of iodotyrosines. The commonly available thionamides are Propylthiouracil (PTU). PTU is generally used to restore euthyroidism before definitive treatment with radioactive iodine and usually before surgery (1,3,6).

PTU can be used in combination with radioactive iodine to accelerate clinical improvement while waiting for the therapeutic effect of radioactive iodine (7). There is known considerable evidence that radiopharmaceutical biodistribution or pharmacokinetics may become altered by a variety of drugs. Remaining ignorant of such factors (interactions-drug interactions) can lead to a state of total disorder(8,9).

The aim of this research was to determine the effect of PTU treatment to pharmacokinetics interaction and biodistribution profile of  $\text{Na}^{131}\text{I}$  radiopharmaceuticals on rats (*Rattus norvegicus*) Sprague dawley stock and interpretate drug-radiopharmaceutical interaction to pharmacokinetics and biodistribution profile of  $\text{Na}^{131}\text{I}$ . The results

are expected could be used by the doctor in nuclear medicine to interpretate imaging result which is intervened by drug interaction.

## 2. METHODS

### 2.1. Materials and Instruments

The materials are Na<sup>131</sup>I solution (BATAN), 100 mg propylthiouracil tablet (Dexa Medica, Corp) suspended with 1% CMC, methanol (Merck), isoflurane, aquabidest (IPHA), Whatman no 1 paper and universal pH paper.

The instruments are single channel analyzer (Ortec), dose calibrator (Victoreen), oven (Memmert), Nuova stirring hot plate (Barnstead Thermolyne), analytical balance (Mettler Toledo), paper chromatography apparatus, vortex (Barnstead Thermolyne), rat restrainer, stomach tube for rats, micro-pipette (Eppendorf) and anaesthesia chamber.

### 2.2. Animals

Eighteen male rats (*Rattus norvegicus*) Sprague dawley stock, with 5 weeks age and 200-300 grams of bodyweight. These tests used three groups of animal model, i.e. experimental animals which given PTU with dose 4.2mg/kg BW/day for 1 time (onset or A groups), animals which given PTU with dose 4.2mg/kg BW/day for six days (B Groups), and animals without treatment (control or C Groups). Animals used in the experiments received care in compliance with the "Principles of Laboratory Animal Care" and "Guide for the care and use of Laboratory Animals".

### 2.3. Radiochemical Purity of Iodine-131

Radiochemical purity of Iodine-131 was determined by ascending paper chromatography method. Chromatography system using Whatmann 1 paper as stationery phase and methanol-water (80:20) as mobile phase to separate impurities(10,11). Paper chromatogram was dried in oven at 80°C for 5 minutes and every 1 cm piece of paper is measured by SCA. Retention factor (Rf) of Iodine-131= 0.8 and impurities at Rf=0.0 (12).

### 2.4. Pharmacokinetics Test

Experimental animals were prepared in three groups which consists of 3 rats each group. Iodine-131 solution with dose 100 µCi/100 µL was given per oral to each animal model. At specific time intervals post giving Iodine-131 solution, blood sampling from tail was performed and weighed, then counted using Single Channel Analyzer. Measurement results were expressed as a percentage of Injection Dose per gram of blood (%ID/g)(13). Calculating of %ID/g using formula (1):

$$\%ID/g = \frac{\text{blood per gram count}}{\text{injected dose count}} \times 100\% \dots\dots (1)$$

The absorption, distribution, and elimination half time of Na<sup>131</sup>I was determined from percentage of Injection Dose per gram of blood, then described in graphic form to obtain the compartment equations. Statistical test using ANOVA (14,15).

## 2.5. Biodistribution Test

Biodistribution test was adopted and modified by Ocakoglu *et al* method. Experimental animals were prepared in three groups which consists of 3 rats each group, then Iodine-131 solution with dose 100  $\mu\text{Ci}/100 \mu\text{L}$  was given by per oral after 1 hour (A groups), and 24 hours (B groups) post giving PTU. Experimental animals were euthanized at 90 minutes post giving Iodine-131 solution with inhaled anaesthetics overdose (isoflurane) then necropted. Specific organs i.e. thyroid gland, muscle, bone, blood, intestine, gastric, liver, spleen, kidney, heart, and lung were collected. Every organs were weighed, then counted using Single Channel Analyzer. Measurement results were expressed as a percentage of Injection Dose per gram of organs (%ID/g) (13). Calculating of %ID/g using formula (2):

$$\%ID/g = \frac{\text{organ per gram count}}{\text{injected dose count}} \times 100\% \dots (2)$$

Percentage of radioactivity in the organ samples was described in the graph and statistical test using ANOVA(15,16).

## 3. RESULT AND BRIEF DISCUSSION

Radiochemical purity of  $\text{Na}^{131}\text{I}$  solution was obtained  $98.42\% \pm 0.003$  ( $n=3$ ) with pH between 8-11 (base solution in NaOH). Based on the results of radiochemical purity (more than 95%),  $\text{Na}^{131}\text{I}$  solution was fulfilled the requirement of Indonesian

Pharmacopoeia and continued to pharmacokinetics and biodistribution test (11). As shown on Figure 1, the peak of iodine-131 at 0.8 retention factor separated from impurities at 0.0 retention factor.

The pharmacokinetic profiles of  $\text{Na}^{131}\text{I}$  radiopharmaceutical shown in Figure 2. Peak of radioactivity on the blood of A, B, and C groups were 0.26, 0.24 and 0.34%. This shows that the pattern of giving iodine-131 per oral has absorption, distribution and elimination pattern, which follows three compartments model. The Peak of A and B groups occur at 3 hours after giving  $\text{Na}^{131}\text{I}$  solution, but on C groups (control) occur at 1 hour post giving  $\text{Na}^{131}\text{I}$  solution. It could be caused PTU delay the absorption of iodine-131 to targeted organ although on statistic comparison there was no significant difference in all groups. The percentage of radioactivity on the blood of A, B, and C groups decreased at 72 hours after giving  $\text{Na}^{131}\text{I}$  solution, 0.070, 0.006 and 0.032% respectively.

From the calculation of radioactivity per gram of blood, acquired biological half-life data which is divided into absorption, distribution and elimination half-life. As shown on Table 1, the results of this research showed that the absorption half time of A, B and C groups were  $3.14 \pm 1.42$ ,  $2.49 \pm 0.49$  and  $2.52 \pm 0.7$  hours respectively. The distribution half time of A, B and C groups were  $10.58 \pm 5.85$ ,  $12.92 \pm 3.75$  and  $11.42 \pm 3.15$  hours respectively.

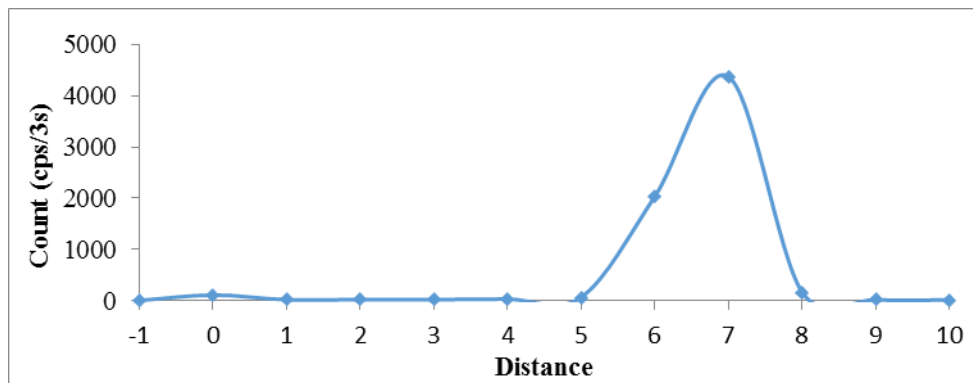


Figure 1. Chromatogram of Iodine-131 using whatman No. 1 paper as stationary phase and methanol-water (80:20) as mobile phase.

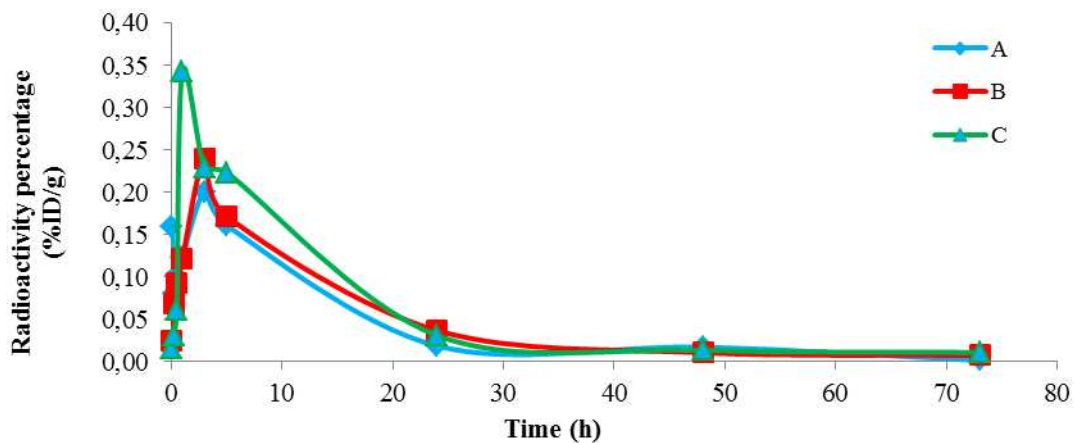


Figure 2. Pharmacokinetics profile of Na<sup>131</sup>I, Experimental animal which giving PTU for 1 time (A Group); Experimental animal which giving PTU for 6 days (B Group) and Control Animal (C Group).

The elimination half time of A, B and C groups were  $113.03 \pm 46.03$ ,  $96.57 \pm 47.76$  and  $196.71 \pm 145.21$  hours respectively. Anova test showed that there were no significant different between A, B and C groups. Although result of anova test show that no significant different between all groups, can be seen on all groups has wide standard deviation. It can be caused by limitation number of the animals that has different physiology system each other. The biodistribution test showed that the biggest accumulation of Na<sup>131</sup>I was on

stomach and thyroid (Table 2). Iodine is a substrate for thyroid hormone synthesis and is actively transported into the thyroid follicular cells by an iodine symporter. It is oxidized and covalently bound to the tyrosyl residues of thyroglobulin (3). Coupling of iodinated tyrosyl residues results in the formation of T<sub>4</sub> and T<sub>3</sub>, which are stored within the colloid space. Radioiodine (<sup>131</sup>I) is similarly processed. In normal thyroid tissue, thyrotropin is required to stimulate iodine uptake into follicular cells.

Table 1. Biological half time of Na<sup>131</sup>I with PTU treatment

Condition	t <sub>1/2</sub> absorption (hours)	t <sub>1/2</sub> distribution (hours)	t <sub>1/2</sub> elimination (hours)
Onset (A)	3.14 ± 1.42	10.58 ± 5.85	113.03 ± 46.03
Long term (B)	2.49 ± 0.49	12.92 ± 3.75	96.57 ± 47.76
Control (C)	2.52 ± 0.10	11.42 ± 4.45	196.71 ± 145.21

Table 2. Biodistribution of Na<sup>131</sup>I

Organ Samples	A group (%)	B group (%)	C group (%)
Muscle	0.065	0.050	0.043
Thyroid	1.315	4.206	4.454
Blood	0.498	0.344	0.231
Intestine	1.557	0.514	0.333
Liver	0.280	0.151	0.270
Spleen	0.268	0.188	0.139
Kidney	0.643	0.231	0.152
Heart	0.205	0.107	0.124
Lung	0.441	0.263	0.293
Stomach	7.929	3.064	4.484
Bone	0.177	0.136	0.101

Radioiodine is processed in a thyroid follicle (3). The thyrotropin receptor and the sodium–iodine symporter (NIS) are located on the basolateral membrane. Iodine is actively transported across the apical membrane in a pendrin-dependent process. In the presence of hydrogen peroxide, thyroid peroxidase facilitates the iodination of the tyrosyl residues of thyroxine. The resulting compound is subsequently coupled to form free thyroxine (T4) and triiodothyronine (T3) (3). NIS is expressed in the thyroid, salivary glands, gastric mucosa, and lactating mammary glands. It is also detected in the lacrimal glands, choroid plexus, ciliary bodies (located in the eyes), skin, placenta, and thymus.

Lower levels of NIS expression are seen in the prostate, ovaries, adrenal glands, lungs, and heart. In the stomach, NIS may

be expressed in parietal cells or mucus cells of the gastric mucosa. NIS expression has been explored as a possible means for providing targeted radionuclide therapy(17).

Biodistribution of Na<sup>131</sup>I on thyroid organs is showed by Figure 3. Results of Anova test on thyroid organs showed there were significant different between A groups (PTU onset) to C groups (Control) and no significant between B groups to C groups. It could be caused on A groups, iodide uptake by thyroid is inhibited 2-3 hours by PTU and on B groups PTU had been excreted.

Benker *et al* explained that antithyroid drugs like PTU has striking discrepancy between short plasma half time and long duration of action of PTU. PTU half time in plasma is 1 hour and undetectable after 7-8 hours. (18).

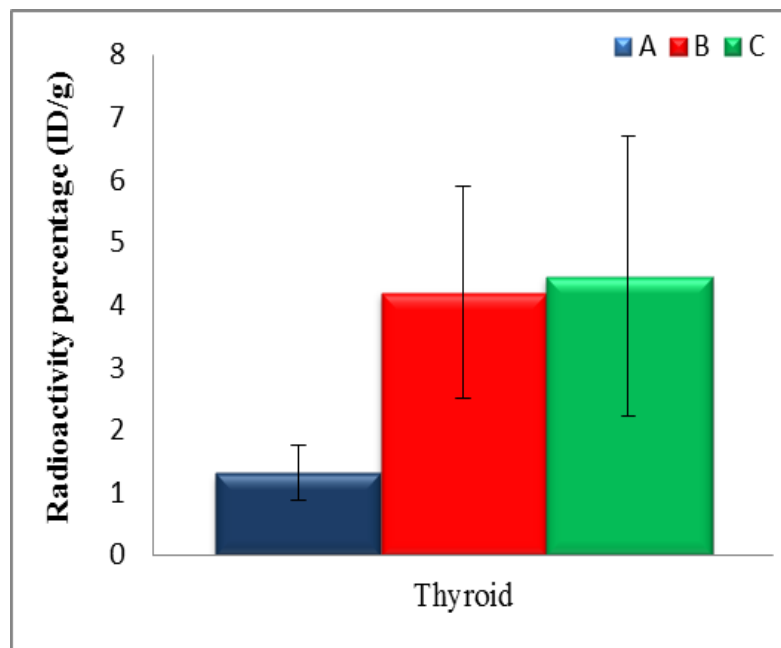


Figure 3. Biodistribution of Na<sup>131</sup>I on thyroid gland (A: Experimental animal which giving PTU for 1 time (Onset); B: Experimental animal which giving PTU for 6 days; C: Control Animal)

PTU has spesific effect to NIS. Montoya *et al* has been explained that PTU inhibit the enzyme thyroperoxidase which normally acts in thyroid hormone synthesis facilitating the addition of iodine to tyrosine residues on the hormone precursor thyroglobulin. This is one of the essential steps in the formation of thyroxine (T4). Significant increase of thyroid-free tyrosine in animals treated with PTU has been due to the decrease of endogenous T4 production and subsequent stimulation of endogenous TSH release. Sue *et al* also reported that PTU coordinately increased NIS promoter activity NIS protein levels. Although NIS protein levels were similarly induced by PTU and TSH. The size of the resulting proteins and their subcellular distribution patterns were different. The fully glycosylated NIS protein migrates with a molecular weight of 87–110 kDa. As such. the observed

differences in molecular weight between PTU- and TSH-induced NIS proteins may reflect post-translational modifications such as glycosylation and phosphorylation so PTU-induced NIS protein was relatively immature compared to TSH-induced NIS protein which could also be consistent with the lower iodide accumulation of the PTU-induced NIS protein. (19,20).

#### 4. CONCLUSION

This research was concluded that PTU for onset or long term treatment cannot alter absorption, distribution and elimination half time (pharmacokinetics profile) of sodium iodide (Na<sup>131</sup>I) radiopharmaceutical and administration PTU in onset for pretreatment can decrease accumulation of Na<sup>131</sup>I on thyroid, different with administration PTU in long term which can not alter accumulation of Na<sup>131</sup>I on thyroid.

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