Distribution of radioactivity and plasma levels of ^{131}I Quinidine after intravenous administration in rats.**

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Abstract:

In this study, Quinidine is labeled with ^{131}I and administered endovenously in Wistar rats. The plasma levels of ^{131}I Quinidine are calculed and the biological distribution is investigated.

Introduction:

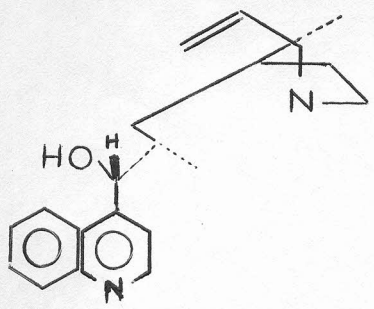
Quinidin is a stereoisomer of quinine and the drug of choice in the treatment of cardiac arrhythmia (1) (2). The purpose of this experiment is labeling of Quinidin with a radioisotope (^{131}I) and the estimation of pharmacological behaviour. The plasma levels and biological distribution of the experimental investigations of Quinidin kinetic: ^{131}I Quinidin removal from the blood and its distribution in organs.

Materials and methods:

Quinidin base - Laboratoire Nativelle - Paris; melting point of the Quinidin base purified: 174-175°C.

Na ^{131}I from "Instituto de Pesquisas Energéticas e Nucleares"-IPEN-CNEN/SP.

Figure 1 - Structure of quinidine.



Isotopic labeling - 20mg of quinidin are dissolved in a mixture of 0,5ml of H_2SO_4 solution (0,8% v/v) and 0,5ml of 0,2M acetate-acetic buffer, pH 5. The final pH was adjusted to 4. Na ^{131}I was added and 0,1ml of perhidrol. The mixture was maintained at room temperature for 30 minutes. The labeled quinidin in solution was precipitated with NaOH N/1 solution, centrifugated and the supernatant separated. The base was redissolved with sulphuric acid and reprecipitated. This operation was repeated two times. The final purified ^{131}I quinidine was dissolved in a mixture of 0,5ml H_2SO_4 (0,8% v/v) and 1ml of 0,2M acetate-acetic acid, pH 5. The final pH was arised to 6.0 - 6.5 with 0.1N NaOH solution. The total volume of the solution was 2.5ml.

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Labeling yield - 40 to 50% after purification.

Radiochemical purity is ascertained by electrophoresis paper (Whatman nº 1) in strips with 1.5 x 35cm; 0.2M acetate-acetic acid pH 5.4; 8V/cm during 45 minutes.

The radioactive measurements was maximal at the position of quinidine ^{131}I spot. Quinidine was vizualized with U.V light.

Animal procedure:

Wistar rats (300g) were used. For plasma and tissue distribution studies, each rat (3 rats in each experiment) was injected with 0.25ml saline solution containing 2mg and 10 µCi ^{131}I Quinidine through the tail vein. Animals were killed at various times after injection. The organs of interest were excised, weighed, and counted in a NaI(Tl) well type scintillation counter along with a diluted standard of injected dose.

Results:

Curve of plasma radioactivity versus time is shown in figure 2. The plasma levels data were expressed by percent concentration described as follows:

$$\% \text{ radioactivity} = \frac{\text{1ml Plasma counts}}{\text{standard counts}} \times 100 \times \frac{\text{Blood volume (100-Hc)}}{100}$$

Hc = corrected haematocrit: observed value x 0,96 x 0.91 (3).

The Plasma decay curve is biexponential.

$$Q_p = Ae^{at} + Be^{-bt}$$

Q_p - is the percentage of ^{131}I-quinidine in plasma at time t.
A^p - the percentage of ^{131}I-quinidine at t=0. The first exponential.
B - the percentage of ^{131}I quinidine at tima=0 - second exponential.
a - the first decay constant.
b - the second decay constant.

The Computer Program "SAS"-76 (Statistic Analysis System-IBM) (4).

A = 0,1243
B = 0,2248
a =33,2406
b = 2,8076

1st. - T/2 = 0,693/33,2406 = 0.0208h (1.25min.).
2nd. - T/2 = 0.693/2.8076 = 0.2468 (14.81min.).

FIGURE 2

MONO-LOG
10
1.0
0.1
0.01
% of Radioactivity / ml of plasma
0
2
4
6
8
10
12
14
16
18
20
22
24
hours
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TABLE

Tissue Distribution Data (% / g). ^{131}I-Quinidine in rats at various time intervals after injection. Mean of three rats.

ORGAN	5 min.	15 min.	30 min.	60 min.	2h	6h	18h	24h
Liver	3.18±0.30	2.13±0.24	1.66±0.01	1.07±0.05	1.16±0.13	0.38±0.6	0.06±0.01	0.05±0.01
Heart	1.36±0.02	0.86±0.16	0.34±0.01	0.22±0.02	0.26±0.02	0.06±0.00	0006±0.00	0.003±0.001
Lungs	4.13±0.22	3.82±0.44	1.44±0.22	1.66±0.08	2.00±0.44	0.49±0.12	0.05±0.01	0.019±0.001
Spleen	2.29±0.47	1.84±0.09	1.10±0.01	1.00±0.02	2.15±0.29	0.37±0.12	0.02±0.004	0.016±0.001
Kidneys	3.91±1.60	2.49±0.07	1.19±0.08	0.73±0.03	0.81±0.10	0.19±0.02	0.02±0.003	0.015±0.003
Large intest	1.58±0.31	0.55±0.03	0.24±0.01	0.17±0.01	0.19±0.03	0.19±0.10	0.02±0.005	0.012±0.005
Small intest	0.32±0.06	1.21±0.53	2.32±0.35	0.76±0.54	1.20±0.25	0.23±0.10	0.02±0.004	0.006±0.001
Stomach	1.40±0.32	0.88±0.07	0.75±0.08	0.73±0.28	0.63±0.10	0.07±0.005	0.033±0.002	0.015±0.001
Pancreas	1.55±0.48	0.77±0.07	0.41±0.04	0.24±0.05	0.33±0.08	0.29±0.16	0.006±0.001	0.003±0.000
Tireoide % organ	0.20±0.10	0.29±0.11	0.36±0.07	0.16±0.02	0.76±0.16	1.29±0.20	0.41±0.11	0.66±0.10

Discussion:

The labeling of quinidin with ^{131}I is possible because these structure present a double bond abble to react with halogens. (5)

There are good reasons for believing that perhidrol don't oxidizes quinidin in a large extension, because the melting point of quinidin base after treatment with perhidrol is conserved (quininone is not formed).

The plasma decay of quinidin ^{131}I shows two T/2 indicating that it involves two conventional body compartments. That is according with the findings of Greenblatt and all (2) and Isaacs and al. (6).

Aviado & Salem (1) presents that quinidin in blood is bound to plasma proteins and the drug is taken up rapidily by all tissues. The authores indicates that quinidin concentrates in heart muscles especially in dogs ^{131}I quinidin was not concentrated in rat heart muscles but we are encountered a high concentration of ^{131}I quinidin in lungs. Probably the lungs receptors are abble to takeup iodinated quinidin (7).

Several authores (1) describe gastrointestinal reaction how sintoms of side effects in the therapeutic use of quinidin. These authors find no correlation between plasma levels of quinidine and the gastrointestinal toxicity. The levels of ^{131}I quinidine in small intestine and stomach (table 1) tissues show some correlation between these organs uptake and the toxicity described.

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