CardioGen-82®

Rubidium Rb 82 Generator

43-8200

For Elution of Rubidium Chloride Rb 82 Injection
Diagnostic: Intravenous

DESCRIPTION

Cardiogen-82® (Rubidium Rb 82 Generator) contains accelerator produced strontium Sr 82 adsorbed on stannic oxide in a lead-shielded column and provides a means for obtaining sterile nonpyrogenic solutions of rubidium chloride Rb 82 injection. The chemical form of rubidium 82 is ^{82}RbCl.

The amount (millicuries) of Rb-82 obtained in each elution will depend on the potency of the generator.

When eluted at a rate of 50 mL/minute, each generator eluate at the end of elution should not contain more than 0.02 microcurie of strontium Sr 82 and not more than 0.2 microcurie of strontium Sr 85 per millicurie of rubidium chloride Rb 82 injection, and not more than 1 microgram of tin per mL of eluate.

PHYSICAL CHARACTERISTICS

Rubidium Rb 82 decays by positron emission and associated gamma emission with a physical half-life of 75 seconds.[1] The annihilation photons released following positron emission which are useful for detection and imaging studies are shown in Table 1.

TABLE 1

Principal Radiation Emission Data

Radiation	Mean Percent Per Disintegration	Mean Energy (keV)
Annihilation photons (2)	191.01	511 (each)

[1]Table of Isotopes, 7th Edition, M. Letterer and V. Shirley.

External Radiation

The specific gamma ray constant for Rb-82 is 6.1 R/hour-millicurie at 1 centimeter. The first half-value layer is 0.7 centimeter of lead (Pb). A range of values for the relative attenuation of the radiation emitted by this radionuclide that results from interposition of various thicknesses of Pb is shown in Table 2. For example, the use of a 7.0 centimeter thickness of Pb will attenuate the radiation emitted by a factor of about 1,000.

TABLE 2

Radiation Attenuation by Lead Shielding

Shield Thickness (Pb) cm	Attenuation Factor
0.7	0.5
2.3	10^{-1}
4.7	10^{-2}
7.0	10^{-3}
9.3	10^{-4}

Strontium Sr 82 decays to rubidium Rb 82 with a strontium Sr 82 half-life of 25 days (600 hrs). The Sr-82 is produced in an accelerator by proton spallation of molybdenum, Mo (p, spall) Sr-82 or by the reaction Rb-85 (p, 4n) Sr-82. The Sr-82 produced has no carrier added. To correct for physical decay of strontium Sr 82, the fractions that remain at selected intervals after the time of calibration are shown in Table 3.

TABLE 3

Physical Decay Chart: Sr-82 half-life 25 days

Days	Fraction Remaining	Days	Fraction Remaining	Days	Fraction Remaining
0*	1.000	11	0.737	21	0.559
1	0.973	12	0.717	22	0.543
2	0.946	13	0.697	23	0.529
3	0.920	14	0.678	24	0.514
4	0.895	15	0.660	25	0.500
5	0.871	16	0.642	26	0.486
6	0.847	17	0.624	27	0.473
7	0.824	18	0.607	28	0.460
8	0.801	19	0.591	29	0.448
9	0.779	20	0.574	30	0.435
10	0.758				

*Calibration time

To correct for physical decay of rubidium Rb 82, the fraction of rubidium chloride Rb 82 injection remaining in all 15 second intervals up to 300 seconds after time of calibration are shown in Table 4.

TABLE 4

Physical Decay Chart: Rb-82 half-life 75 seconds

Seconds	Fraction Remaining	Seconds	Fraction Remaining
0*	1.000	165	.218
15	.871	180	.190
30	.758	195	.165
45	.660	210	.144
60	.574	225	.125
75	.500	240	.109
90	.435	255	.095
105	.379	270	.083
120	.330	285	.072
135	.287	300	.063
150	.250		

*Elution time

CLINICAL PHARMACOLOGY

Following intravenous administration, rubidium Rb 82 rapidly clears the blood and is extracted by myocardial tissue in a manner analogous to potassium. In human studies, myocardial activity was noted within the first minute after injection. When areas of myocardial infarction are detected with rubidium chloride Rb 82 injection, they are visualized within two to seven minutes after injection as photon-deficient or "cold areas" on the myocardial scan. Uptake is also observed in kidney, liver, spleen, and lung.

INDICATIONS AND USAGE

Rubidium chloride Rb 82 injection is a myocardial perfusion agent that is useful in distinguishing normal from abnormal myocardium in patients with suspected myocardial infarction.

Cardiogen-82 (Rubidium Rb 82 Generator) must be used with an infusion system specifically labeled for use with the generator and capable of accurate measurement and delivery of doses of rubidium chloride Rb 82 injection not to exceed a single dose of 2220 MBq (60 mCi) and a cumulative dose of 4440 MBq (120 mCi) at a rate of 50 mL/min with a maximum volume per infusion of 100 mL and a cumulative volume not to exceed 200 mL. These performance characteristics reflect the conditions of use under which the drug development clinical trials were conducted.

Adequate data from clinical trials to determine precise localization of myocardial infarction or identification of stress-induced ischemia have not been collected.

Positron emission tomographic (PET) instrumentation is recommended for use with rubidium chloride Rb 82 injection.

CONTRAINDICATIONS

None known.

WARNINGS

Caution should be used during infusion as patients with congestive heart failure may experience a transitory increase in circulatory volume load. These patients should be observed for several hours following the Rb-82 procedure to detect delayed hemodynamic disturbances.

PRECAUTIONS

General

Data are not available concerning the effect of marked alterations in blood glucose, insulin, or pH (such as is found in diabetes mellitus) on the quality of rubidium chloride Rb 82 scans. Attention is directed to the fact that rubidium is physiologically similar to potassium, and since the transport of potassium is affected by these factors, the possibility exists that rubidium may likewise be affected.

Rubidium chloride Rb 82 injection must be administered only with an appropriate infusion system capable of meeting the performance characteristics previously described. (See **INDICATIONS AND USAGE**). The drug should be used only by those practitioners with a thorough understanding of the use and performance of the infusion system.

Repeat doses of Rubidium chloride Rb 82 injection may lead to an accumulation of the longer lived radioactive contaminants strontium Sr 82 and strontium Sr 85.

Since eluate obtained from the generator is intended for intravenous administration, aseptic techniques must be strictly observed in all handling. Only additive free Sodium Chloride Injection USP should be used to elute the generator. Do not administer eluate from the generator if there is any evidence of foreign matter.

As in the use of any radioactive material, care should be taken to minimize radiation exposure to the patient consistent with proper patient management and to insure minimum radiation exposure to occupational workers.

Radiopharmaceuticals should be used only by physicians who are qualified by training and experience in the safe use and handling of radionuclides and whose experience and training have been approved by the appropriate government agency authorized to license the use of radionuclides.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No long-term studies have been performed to evaluate carcinogenic potential, mutagenicity potential, or to determine whether rubidium Rb 82 may affect fertility in males or females.

Pregnancy Category C

Animal reproductive studies have not been conducted with rubidium Rb 82. It is also not known whether rubidium Rb 82 can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Rubidium Rb 82 should be given to pregnant women only if the expected benefits to be gained clearly outweigh the potential hazards.

Ideally, examinations using radiopharmaceuticals, especially those examinations which are elective in nature, in women of childbearing capability should be performed during the first few (approximately 10) days following the onset of menses.

Nursing Mothers

It is not known whether rubidium Rb 82 is excreted in human milk. Due to the short half-life of rubidium Rb 82 (75 sec) it is unlikely that the drug would be excreted in human milk during lactation. However, because many drugs are excreted in human milk, caution should be exercised when rubidium Rb 82 is administered to nursing women.

Pediatric Use

Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

No adverse reactions specifically attributable to rubidium Rb 82 have been reported during controlled clinical trials.

DOSAGE AND ADMINISTRATION

General

As with all radiopharmaceuticals, only the lowest dose of rubidium Rb 82 necessary to obtain adequate visualization should be used. A lower dose provides less patient radiation and is consistent with the achievement of ALARA. Most procedures do not require use of the maximum dose of rubidium Rb 82; the dose to be used should be carefully individualized and factors such as:

age;
body size;
anticipated pathology;
degree and extent of visualization required;
structure(s) or area to be examined;
disease processes affecting the patient and;
equipment and technique to be employed;

should be considered.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

An appropriate infusion system labeled for use with Cardiogen-82 (Rubidium Rb 82 Generator) is required. Please see DIRECTIONS FOR ELUTING RUBIDIUM CHLORIDE Rb 82 INJECTION below for additional information. (See also **INDICATIONS AND USAGE**).

Rubidium Rb 82 assay and strontium Sr 82 breakthrough should be determined each day the generator is used (See directions below).

Rubidium-82 Dosage

Rubidium chloride Rb 82 injection obtained from Cardiogen-82 (Rubidium Rb 82 Generator) is intended only for intravenous administration utilizing an appropriate infusion system that is labeled for use with the generator. The usual adult (70 kg) dose (single injection) is 1480 MBq (40

mCi) with a range of 1110-2220 MBq (30-60 mCi). The dose must be administered at a rate of 50 mL/minute not to exceed a cumulative volume of 200 mL. (See also **WARNINGS**).

A single dose of 2220 MBq (60 mCi) should not be exceeded. The radiation dosimetry for a 2220 MBq (60 mCi) dose is presented in Table 5. No more than 4440 MBq (120 mCi) should be administered in a multiple injection series.

Exceeding the recommended dosing limits should only be done after due consideration of: (a) the benefits to be obtained by the patient vs. the risks associated with additional radiation; (b) previous (or contemplated) procedures involving radiation which this patient has undergone or might undergo; and (c) the achievement of ALARA. Further consideration should be given to the effect of total volume of injectate, which increases with the number of injections, as discussed under **WARNINGS**.

Radiation Dosimetry

The estimated absorbed radiation doses to an average adult patient (70 kg) from an intravenous injection of a recommended dose of 2220 MBq (60 mCi) of rubidium Rb 82 are shown in Table 5.

TABLE 5

Adult Absorbed Radiation Doses[1]

Organ	mGy/2220 MBq	rads/60 mCi
Adrenals	2.15	0.22
Stomach	1.91	0.19
Small Intestine	3.11	0.32
Upper Large Intestine	1.91	0.19
Lower Large Intestine	1.91	0.19
Heart Wall	4.22	0.42
Kidneys	19.1	1.92
Liver	1.91	0.19
Lungs	3.77	0.38
Ovaries	0.84	0.084
Pancreas	1.38	0.14
Trabecular Bone	0.0055	0.00055
Cortical Bone	0.0091	0.0009
Red Marrow	0.84	0.084
Testes	0.67	0.066
Total Body	0.95	0.096

[1]Calculated by the Internal Dosimetry Center at Oak Ridge Associated Universities

Based on data collected by Ryan et al. in two human subjects (**J Nuc Med** 25(5): P94) and on rat data of Kearfott (**J Nuc Med** 23(12):1128-1132. Contaminant levels of Sr-82 and Sr-85 assumed to be 10^{-7} and 2.5 X 10^{-7} relative to Rb-82.

For strontium, assumed distribution and retention:

Bone	50% t_b = ∞ (uniformity distributed throughout volume)
Testes	0.5% t_b = 1.5 day
Remainder	49.5% t_b = 1.5 day

HOW SUPPLIED

Cardiogen-82® (Rubidium Rb 82 Generator) is supplied in the form of strontium Sr 82 adsorbed on a hydrous stannic oxide column with an activity of 90-150 millicuries Sr-82 at calibration time. The generator is encased in a lead shield surrounded by a labeled plastic container. Complete assay data for each generator are provided on the container label. Directions for determining the activity of rubidium Rb 82 eluted from the generator are provided in this monograph. Cardiogen-82 (Rubidium Rb 82 Generator) is intended for use only with an appropriate, properly calibrated infusion system labeled for use with the generator.

Receipt, transfer, handling, possession or use of this product is subject to the radioactive material regulations and licensing requirements of the U.S. Nuclear Regulatory Commission, Agreement States or Licensing States as appropriate.

DISPOSAL

Hospital personnel should monitor the amount of radioactivity present at the generator prior to its disposal. The generator should not be disposed of in regular refuse systems. Storage and/or disposal of the generator should be in accordance with the conditions of NRC radioactive materials license pursuant to 10 CFR, Part 20, or equivalent conditions pursuant to Agreement State Regulation.

STORAGE

The generator should be stored at 20-25°C (68-77°C) [See USP].

EXPIRATION DATE

The expiration date is provided on the generator container label. Due to the short half-life of Rb-82, virtually all the radioactivity in the eluate decays within 15 minutes from the end of elution.

DIRECTIONS FOR ELUTING RUBIDIUM Rb 82

An appropriate infusion system labeled for use with Cardiogen-82 (Rubidium Rb 82 Generator) is required. The applicable operator's manual should be consulted for detailed directions on generator hookup, elution, and patient administration. Prior to use with patients, a thorough understanding of the use and performance of the system should be established.

The Cardiogen-82 (Rubidium Rb 82 Generator) package insert and the Rb-82 infusion system operator's manual should be read before beginning elution.

Additional information concerning eluting the Cardiogen-82 generator follows:

NOTE: Waterproof gloves are to be worn during the preparation and elution processes.

Aseptic techniques should be employed throughout the preparation and elution processes.

Allow at least 10 minutes between elutions for regeneration of Rb-82.

Elute with additive free Sodium Chloride Injection USP only.

Discard the first 50 mL eluate each day the generator is eluted. Since the eluate contains radioactivity, it must be handled employing proper safety precautions.

DIRECTIONS FOR DETERMINATION OF Rb-82 ASSAY AND MEASUREMENT OF Sr-82 AND Sr-85 BREAKTHROUGH

The rubidium chloride Rb 82 assay and strontium Sr 82 and strontium Sr 85 breakthrough are determined using an ionization chamber-type dose calibrator. Procedure 1 through 11 below must be performed daily prior to the use of rubidium chloride Rb 82 injection.

The assay of rubidium chloride Rb 82 injection is determined as follows:

1. Set a dose calibrator for Rb-82 as recommended by the manufacturer or use the Co-60 setting and divide the reading obtained by 0.548. Obtain the reading from the instrument in millicuries.
2. Aseptically elute the generator with 50 mL of Sodium Chloride Injection USP and discard the eluent (first elution).
3. After allowing at least 10 minutes for the regeneration of Rb-82, aseptically elute the generator with 50 mL of Sodium Chloride Injection USP at a rate of 50 mL/min and collect the eluate in a stoppered glass vial (plastic containers are not suitable). Note the exact time of end of elution (E.O.E.).
4. Using the dose calibrator, determine the activity of Rb-82 and note the time of the reading. Correct the reading for decay to the E.O.E. using the appropriate decay factor for Rb-82 (see Table 4). Note: If the reading is taken $2\frac{1}{2}$ minutes after E.O.E. decay correction can be made by multiplying the dose calibrator reading by 4.

To measure the Sr-82 breakthrough in the eluate, proceed as follows:

5. Using the sample obtained for the Rb-82 activity determination, allow the sample to stand for at least one hour to allow for the complete decay of Rb-82.
6. Measure the activity of the sample in a dose calibrator at the setting recommended by the manufacturer for Rb-82 and/or Sr-82. As an alternative the Co-60 setting may be used and the reading obtained divided by 0.548. Obtain the reading from the instrument in microcuries.
7. Calculate the ratio (R) of Sr-85/Sr-82 on the date of measurement using the Sr-85/Sr-82 ratio chart below (Table 6) and the ratio of Sr-85/Sr-82 on the day of calibration provided on the generator label. Determine R using the following equation:

$$R = \frac{[Sr\text{-}85]}{[Sr\text{-}82]} \text{ on calibration date x ratio factor on the date of measurement}$$

8. Use a correction factor (F) of 0.478 to compensate for the contribution of Sr-85 to the reading.
9. Calculate the amount of Sr-82 in the sample using the following equation:

$$\text{Sr-82 } (\mu\text{Ci}) = \frac{\text{dose calibration reading } (\mu\text{Ci})}{[1 + (R)\ (F)]}$$

Example: dose calibrator reading (µCi) = 0.80

Sr-85/Sr-82 ratio (R) = (1.48)

Correction factor (F) = 0.478

$$\text{Sr-82 } (\mu\text{Ci}) \quad \frac{0.80}{[1 + (1.48)(0.478)]}$$

Sr-82 (µCi) = 0.47

10. Determine the Sr-82 breakthrough by dividing the µCi of Sr-82 by the mCi of Rb-82 at E.O.E.

Example:

0.47 µCi of Sr-82

50 mCi of Rb-82 E.O.E.

$$\frac{0.47\ \mu\text{Ci Sr-82}}{50\ \text{mCi Rb-82}} = 0.0094 = 9.4 \times 10^{-3}\ \mu\text{Ci/mCi Rb-82}$$

The Sr-82 content must not be more than 2 x 10^{-2} µCi/mCi of Rb-82 at E.O.E.

11. Determine the Sr-85 breakthrough by multiplying the result obtained in step 10 by (R) Sr-85/Sr-82 ratio.

Example:

9.4 x 10^{-3} x 1.48 = 1.4 x 10^{-2} µCi Sr-85/mCi Rb-82

The Sr-85 content must not be more than 0.2 µCi/mCi of Rb-82 at E.O.E.

TABLE 6

Sr-85/Sr-82 Ratio Chart

Days	Ratio Factor	Days	Ratio Factor
0*	1.00	16	1.31
1	1.02	17	1.34
2	1.03	18	1.36
3	1.05	19	1.38
4	1.07	20	1.41
5	1.09	21	1.43
6	1.11	22	1.46
7	1.13	23	1.48
8	1.15	24	1.51
9	1.17	25	1.53
10	1.19	26	1.56
11	1.21	27	1.59
12	1.23	28	1.61
13	1.25	29	1.64
14	1.27	30	1.67
15	1.29		

*Day of calibration

Rx only

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