ing for a short time to reduce the radiation dose, as shown in Tables 3 and 4.

The data presented provide further information on the secretion rate for ^{201}Tl in breast milk and may be helpful in establishing safety guidelines for cases involving ^{201}Tl administration to lactating patients.

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Pharmacokinetics and Dosimetry of Cobalt-55 and Cobalt-57

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The isotopes ^{55}Co and ^{57}Co have been evaluated for PET and SPECT imaging in several clinical brain studies. For clinical application of cobalt, it is important to know the delivered radiation dose. The biodistribution of ^{55}Co in both rat and humans after intravenous (bolus)-administration was studied. Based on pharmacokinetic data, radiation dose calculations according to the MIRD system are presented. By combining present measurements with literature data on $^{60}CoCl_2$, the radiation dose delivered by $^{56}CoCl_2$ ($T_{1/2}$ 78.8 days) and $^{57}CoCl_2$ ($T_{1/2}$ = 270 days) could be assessed. **Methods:** Whole-body Co-PET was performed in two healthy volunteers and one rat after intravenous injection of 37 and 3.7 MBq (1 resp. 0.1 mCi) ^{55}Co, respectively. Blood samples were withdrawn during 300 min in humans. In seven rats the ^{55}Co-biodistribution was determined by postmortem analysis. The residence time of the liver (critical organ) was determined in rats and humans. Blood partition-data of ^{55}Co were assessed resulting in basic pharmacokinetic data in humans. Based on these kinetic data, radiation dose was calculated using the MIRD protocol. **Results:** In both the humans and the rat, the liver and bladder retained the highest fractions of ^{55}Co (about 50% resp. 40% of the administered dose). The liver residence time in humans was 8.6 hr. The free fraction ^{55}Co in the human plasma was at maximum 12%. The total-body mean transit time was 152 min. The volume of the central compartment = 2.8 liter and the steady-state distribution volume = 48 liter. **Conclusion:** From these results, according to the WHO recommendations for class II studies, 22.2 MBq (0.6 mCi) ^{55}Co and 14.8 MBq (0.4 mCi) ^{57}Co (excluding any radionuclide contamination) can be used.

Key Words: cobalt-55; cobalt-57; pharmacokinetics; dosimetry

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In the past, cobalt isotopes have been used for radiotherapy (^{60}Co) and radio-diagnostic purposes (bleomycine-^{57}Co) (*1–4*). Presently, the isotopes ^{55}Co and ^{57}Co are evaluated for brain imaging in several diseases, including stroke, brain trauma and multiple sclerosis (*5–8*). These studies show the potency of cobalt to detect (small) brain lesions. Because of the limited availability of PET centers, we included both ^{55}Co (PET-isotope; $T_{1/2}$ = 17.5 hr) and ^{57}Co (SPECT-isotope; $T_{1/2}$ = 270 days) in our study. Cobalt-55-PET has the advantage of high spatial resolution, absolute quantitation and a relative low radiation dose. The disadvantage is low availability for clinical routine application and logistical problems concerning the relatively short half-life. In contrast, ^{57}Co-SPECT has the disadvantage of a lower spatial resolution, a lack of quantitative representation due to the impossibility of attenuation correction and a relatively high radiation dose. The advantage, however, is its wider availability and simple logistics due to a much longer half-life. Cobalt-55 is commonly produced by the ^{56}Fe (p,2n)^{55}Co nuclear reaction using natural iron as target material (*5*). Since the ^{56}Fe(p,n)^{56}Co reaction is unavoidable, ^{56}Co will always be present as a longer-lived contamination (*4,5*).

For the clinical applications of these cobalt radionuclides, it is important to estimate the radiation dose to various tissues. To specify such dose commitments, knowledge of excretion, retention and distribution of cobalt in man is essential. Such information in man is limited, except that of cobalt as a complex in vitamin B_{12} and bleomycine (*1,9,10*). Virtually all available animal data on free (noncomplexed) cobalt were obtained with ^{60}Co in rats (*9–16*).

In the present study, the in vivo distribution of ^{55}Co following a (single) intravenous-bolus administration of ^{55}Co was studied both in healthy volunteers and in rats. Cobalt-55 blood partition-data were determined. Data obtained from biodistribution, in both rat and humans combined with basic pharmacokinetics of cobalt, were used to calculate the absorbed dose of $CoCl_2$ according to the MIRD formulation (*21*).

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MATERIALS AND METHODS

Cobalt PET

Whole-body scans were made 0–48 hr after the intravenous administration of 37 MBq (1 mCi) sterile $^{55}CoCl_2$. Contiguous scans were made and image reconstruction of 3.375-mm thick planes was done using standard software. The positron camera is calibrated in absolute terms and also cross calibrated with a NaI well counter for the measurement of blood samples. Cobalt-55 was produced by the $^{56}Fe(p,2n)^{55}Co$ nuclear reaction using a 27-MeV proton beam delivered by the AVF-cyclotron of the Technical University of Eindhoven (*2–5*). Purification and quality control have been described in detail elsewhere (*2–5*). The clinical use of ^{55}Co ($T_{1/2}$ 17.5 hr; 77% β^+) is limited due to the contamination with ^{56}Co ($T_{1/2}$ 78.8 days; 19% β^+). The ratio ^{55}Co versus ^{56}Co depends on the energy of the proton beam and the target-thickness used for production. Thus, the radiation dose of both $^{55}CoCl_2$ and $^{56}CoCl_2$ must be assessed. Whole-body scans were made in two volunteers and one rat at various times after intravenous injection.

Animal Studies

Adult male Wistar rats (n = 7) were individually housed with ad libitum access to food and water. Each animal was first provided with a permanent Silicon catheter (0.95 mm o.d.; 0.50 mm i.d.) in the right atrium, inserted via the jugular vein (*17*). This method allows frequent blood-sampling in undisturbed, freely moving rats (*17*). The heart-catheter was permanently fixed to the back of the animal. A week after surgery, animals were injected with 3.7 MBq (0.1 mCi) ^{55}Co through this catheter in a volume of 0.3 ml per animal (t = 0). One rat was anesthetized with pentobarbital (50 mg/kg, ip) and PET scans were made at 0.5, 24 and 48 hr postadministration (pa). Data were analyzed using ^{55}Co liver-residue detection and expressed as arbitrary units (au) per pixel. Rats were killed at t = 55 hr. The counts per minute (cpm) per gram sample were determined in tissue of decapitated animals using a scintillation counter. Tissue samples were taken of urine, kidney, lung, heart, testis, liver, pancreas, blood, spleen, stomach and skin. The animal experiments were approved by the Animal Ethics Committee of the Groningen University.

Healthy Volunteer Studies

Two healthy volunteers (male, age 26–30 yr; 75 and 85 kg body weight) were injected intravenously with 37 MBq (1 mCi) $^{55}CoCl_2$. Of each volunteer three whole-body scans were made: the first immediately, the second at 24 hr and the third at 48 hr after injection. The data acquisition time was 3 min per position and the volunteer was scanned in two parts to cover the whole body. From the reconstructed transverse section images whole body anterior-posterior (AP) views were created using standard software. Blood samples were withdrawn at regular intervals, during 300 min following intravenous administration for ^{55}Co-determination in blood, plasma and the free, cell and protein-bound fraction using dialysis or tri-chloric acid (TCA) precipitation. Sampling was performed using a radial-artery catheter during the first 60 min, followed by venous sampling. The study was approved by the hospital's medical ethics committee and both subjects gave written informed consent.

Human Pharmacokinetics

Cobalt-55 levels were determined in whole blood and plasma. Blood-partition data (cell, protein-bound and free fraction) after a single intravenous bolus administration of 37 MBq (1 mCi) ^{55}Co were obtained. The free fraction was assessed using either dialysis (against phosphate buffered saline; vol:vol: 1:10 and 1:100) or TCA-precipitation (equal volumes of plasma and TCA; and concentration of TCA 15%). Plasma concentration time curves of two human volunteers were analyzed by using a nonlinear regression program (*18*). Data were weighted reciprocally and were fitted best according to a linear open two compartment model. Applying statistical moment theory, basic pharmacokinetic parameters were calculated (*19,20*). The plasma-volume was calculated according to the empirical equation:

$$V_{blood} = 0.417\ (\text{length in meters})^3 + 0{,}045\ (\text{weight in kg-}0{,}03) \times 1000$$

$$V_{plasma} = H_t \times V_{blood}$$

with: V_{blood} = bloodvolume (ml)

V_{plasma} = plasmavolume (ml)

H_t = hematocrite.

Human Dosimetry

To determine the radiation dose of $^{55}CoCl_2$ according to the MIRD protocol the residence times of ^{55}Co in the various organs have to be estimated (*21*). For the calculation of the radiation dose the MIRDOSE3 program was used (*22*). For pharmacokinetic reasons, only three source organs were considered: liver, bladder and gastro-intestinal (gi) tract (*23–27*). The liver is assumed to be the dose-limiting organ since 50% of the administered dose is accumulated in the liver. The time-activity curve of the liver could be described by a monoexponential curve. From this monoexponential liver time-activity curve the T_{eff} is determined, resulting in the liver biological half-life T_b according to:

$$T_{eff}^{-1} = T_b^{-1} + T_{1/2}^{-1}$$

with T_{eff} = effective half-life (liver)

T_b = biological half-life (liver)

$T_{1/2}$ = physical half-life.

From this established T_b and the known $T_{1/2}$ of ^{56}Co and ^{57}Co, T_{eff} of ^{56}Co and ^{57}Co is calculated. Consequently, the liver residence time (T_{res}) can be calculated according:

$$A_0\ T_{res} = \int A_t\ dt$$

$$A = 0.5\ A_0\ e^{-\lambda t}$$

$$\lambda = \ln 2\ T_{eff}^{-1}$$

here A_t = Co activity in the liver at time t, A_0 = administered Co activity intravenously and λ = Co clearance rate from the liver.

Input to the program were the calculated residence time in the liver (T_{res}) in combination with a dynamic bladder model according to the MIRD. A renal input fraction of 40% (based on rat data), a renal T_b (resulting in renal T_{eff}) and the assumption of a voiding interval of 2.5 hr were used as input parameters for the bladder model. For the calculation of the radiation dose in the gi-tract an input fraction of 0.05 into the small intestine (based on rat data) was assumed. The MIRDOSE3 program provides three different estimates, the total body radiation dose (*22*), the effective dose (*28*) and the effective dose equivalent (*29*). The use of total body dose should be restricted to compounds with a rather homogeneous distribution and can only be used as a zero order approximation if no or too few pharmacokinetic parameters are known (*30*). For the calculation of the radiation doses of longer lived Co-isotopes (^{56}Co; ^{57}Co), the fact that a second longer lived compartment in the liver is present has to be taken into account. From measurements

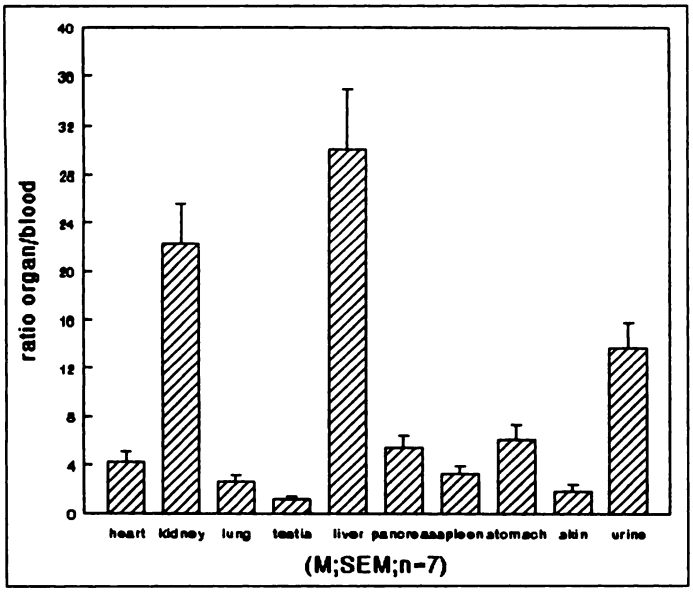

FIGURE 1. Biodistribution of $^{55}CoCl_2$ of the various tissues in the rat (n = 7) following intravenous bolus-administration of 3.7 MBq (0.1 mCi). Data are represented as organ ± blood ratios. The liver and urinary tract evidently account for most of the cobalt accumulation. Rats were killed 55 hr pi.

with $^{60}CoCl_2$ it is known that 9% to 16%, average 12.5%, of the administered dose is present in this compartment (*9–16*). This second compartment is taken into account for the calculation of the radiation dose by assuming 12.5% of the administered dose to be present. The respective residence times can then be calculated according to: $A_0 \times T_{res} = 0.5\ A_0[0.875\ \lambda_1^{-1} + 0.125\ \lambda_2^{-1}]$. From literature on $^{60}CoCl$ a T_b of about 1 yr can be established for the long-lived compartment, resulting in a T_{eff} = 60 days for $^{56}CoCl_2$ and T_{eff} = 140 days for $^{57}CoCl_2$ (*12,23,24,27*).

RESULTS

Rat Studies

After intravenous administration, all tissues showed rapid ^{55}Co uptake, but the liver and bladder accumulated most of the ^{55}Co. The liver data of the rat measured with PET at 0.5, 12, 24 and 48 hr after injection were fitted by a monoexponential curve with an effective half-life T_{eff} = 10.4 hr, resulting in a biological half-life T_b = 25.5 hr. The T_{res} of the rat liver was 7.5 hr. The postmortem distribution of radioactivity over the various individual organs as expressed as blood ratios of ^{55}Co 55 hr after intravenous administration is shown in Figure 1. A substantial amount (about 50%) of the injected dose was associated with the liver, which seems the dose-limiting (critical) organ. The (continuously) collected urine contained 40% of the administered activity, whereas in the (also continuously) collected feces 5% of the administered dose was found.

Human Study

Plasma ^{55}Co levels were measured with respect to time following administration of a single dose of 37 MBq (1 mCi) ^{55}Co. Cobalt-55 is rapidly cleared from the plasma with a (total body) clearance of 315 ml/min. After 3 days ^{55}Co was no longer detectable in the plasma. Cobalt-55 was found predominantly attached to leukocytes and/or plasma-protein. In fact, ^{55}Co was detected to no greater extent than 12% as a free fraction (TCA: 11.8%; 1:10 dialysis 6.0%; 1:100 dialysis 4.7%). Analysis of the plasma concentration-time curve of the free-fraction ^{55}Co following TCA-precipitation revealed a (total body) mean residence time of 152 min with a half-life of the distribution phase (initial phase) of $t_{1/2,\alpha}$ = 1.0 min and a half-life of the elimination phase (terminal phase) of $t_{1/2,\beta}$ = 123 min. The volume of the central compartment was V_1 = 2.8 liter and the volume of distribution in steady state was V_{ss} = 48 liter. The half-lives of the various Co-isotopes are presented in Table 1. In Figure 2, the AP views of the whole-body scans made at 0.5 (A), 24 (B) and 48 hr (C) after injection are shown. The fraction of the injected dose absorbed by the liver amounted to 50%. In the 30-min image (A), renal excretion is already visible.

TABLE 1
Cobalt Half-lives in Human Liver

	$T_{eff,short}$	$T_{eff,short + long}$	$T_{1/2}$	T_b	$T_{res,short}$	$T_{res,short + long}$
^{55}Co	11.9 hr	—	17.5 hr	37.6 hr	8.6 hr	—
^{56}Co	36.9 hr	60 days	78.8 days	37.6 hr	26.6 hr	137 hr
^{57}Co	37.4 hr	140 days	270 days	37.6 hr	27.0 hr	325 hr

T_{eff} = effective half-life (liver); T_b = biological half-life (liver); $T_{1/2}$ = physical half-life; $T_{res,short}$ = Co-residence time in the liver taking only the short-lived compartment into consideration; $T_{res,short + long}$ = Co-residence time in the liver taking the combination of short- and long-lived compartment into consideration.

DISCUSSION

To determine the dosimetry of any cobalt isotope, knowing the residence times T_{res} in the critical organs is essential. Using the values of liver-burden in man, derived from T_{res}, calculations can be made considering the dose which will be delivered to the human liver. We assumed instantaneous deposition of ^{55}Co and the liver-residue curve to be uninterrupted by recirculation of ^{55}Co. Cobalt-55 uptake is rapid compared to decay and removal rates. After administration of ^{55}Co intravenously, a fraction of 0.45 is assumed to go directly to excretion based on animal data. Based on our own findings, a fraction of 0.5 was found to accumulate in the liver. Of ^{55}Co translocated from the liver to other organs and tissues, it is assumed to be both uniformly distributed and to be negligible from a radiological protection point of view. We believe that an estimate of the dose commitment to the total body can be obtained by considering only the liver burden in combination with the bladder and gi burden. The chemical form in which ^{55}Co is retained in the liver and—in low doses—in extrahepatic tissues including the kidneys, gonads and thymus has not been determined.

From the output of the MIRDOSE3 program, it is obvious that the liver dose is by far the largest organ dose, as also can be concluded from the S-factor, $S_{liver \rightarrow liver}$ = 6.23E − 5

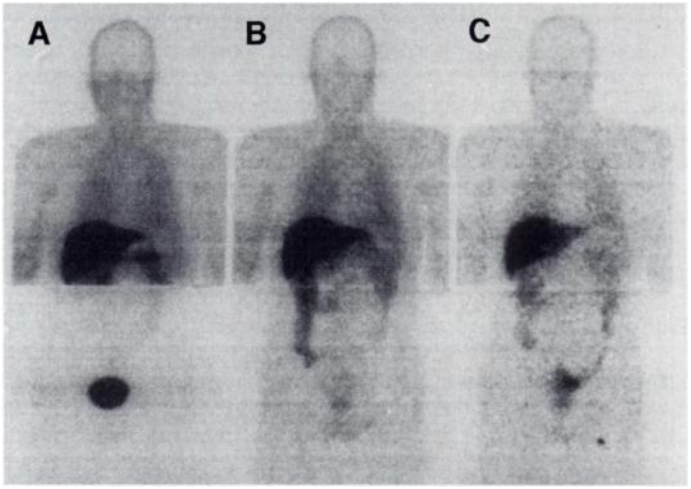

FIGURE 2. Whole-body cobalt-PET of a healthy volunteer at t = 0.5 hr (A), t = 24 hr (B) and t = 48 hr (C) demonstrating rapid cobalt-accumulation in the liver and bladder. The healthy brain evidently does not show cobalt uptake.

TABLE 2
Radiation Dose Delivered by $^{55}CoCl_2$, $^{56}CoCl_2$ and $^{57}CoCl_2$*

Tracer	Total body	ED	EDE
$^{55}CoCl_2$	8.28E-2 (0.31)	1.39E-1 (5.1)	1.89E-1 (0.7)
$^{55}CoCl_2$ + bladder	8.43E-2 (0.31)	1.52E-1 (5.6)	1.97E-1 (0.73)
$^{55}CoCl_2$ + bladder + GI tract	9.16E-2 (0.34)	2.15E-1 (8.0)	2.36E-1 (0.87)
$^{56}CoCl_2$	3.00E-1 (1.1)	4.56E-1 (1.7)	6.75E-1 (2.5)
$^{56}CoCl_2$ + bladder	3.05E-1 (1.1)	4.79E-1 (1.8)	6.81E-1 (2.5)
$^{56}CoCl_2$ + bladder + GI tract	3.27E-1 (1.2)	6.18E-1 (2.3)	7.41E-1 (2.7)
$^{56}CoCl_2$ + bladder + GI tract, T_{res} = 137 hr	1.57E + 0 (5.8)	2.51E + 0 (9.3)	3.54E + 0 (13.1)
$^{57}CoCl_2$ + bladder + GI tract, T_{res} = 325 hr	2.02E-1 (0.75)	3.36E-1 (1.2)	4.65E-1 (1.7)

*Parameters of the dynamic bladder model and gi model are as described in the text. Radiation dose is given as total body dose, effective dose (ED) according to ICRP 60 and effective dose equivalent (EDE) according to ICRP 30. All radiation doses are given in mGy/MBq (rem/mCi) as calculated by the MIRDOSE3 program.

mGy/MBq · s, the fraction of 50% and the residence time (8.6 hr). From Table 2, it is obvious that the contribution of the cobalt excreted via kidneys, using the dynamic bladder model, to the radiation dose is rather limited. Variation in the input parameters of the dynamic bladder model did not imply any significant change in the radiation dose.

The contamination of ^{55}Co with ^{56}Co is unavoidable, due to the production process. The amount of ^{56}Co as percentage of total amount of Co-activity produced is dependent on the proton beam energy and the thickness of the target material. The ^{56}Co contamination can be reduced drastically by using the $^{54}Fe(d,n)^{55}Co$ or the $^{58}Ni(p,\alpha)^{55}Co$ nuclear reaction at the cost of using enriched (rather expensive) ^{54}Fe or ^{58}Ni as a target material and at the cost of a reduced ^{55}Co yield with respect to the proton induced reaction on ^{56}Fe. Cobalt-57 is commercially available without any contamination.

We used a linear open two-compartment model to fit our pharmacokinetic cobalt data. Since the total-body mean transit time T is determined by both $t_{1/2\alpha}$ (initial phase) and $t_{1/2,\beta}$ (elimination phase), and $t_{1/2,\alpha}$ (1 min) is small compared to $t_{1/2,\beta}$ (123 min), the total body T (152 min) is in the same order of magnitude as $t_{1/2,\beta}$ (123 min), which purports cobalt excretion as the rate-limiting process. Moreover, V_1 (volume of the central compartment; 2.8 liter) is in the same order of magnitude as the calculated plasma volume (3 liters) for our healthy volunteers. This suggests the plasma-compartment to be the central cobalt compartment. The (apparent) volume of distribution in steady-state (Vss) is 48 liters, which may be explained by massive accumulation of cobalt in the liver. Our blood-partition data of ^{55}Co represent the average values of 20 samples taken in a period of 300 min postinjection. Although there may be some difference in blood partition in relation to time, these differences were not statistically significant. The cobalt injected into the blood was predominantly retrieved attached to leukocytes and plasma protein. Less than 12% of the blood cobalt could be recovered from the protein-free plasma. Protein precipitation by TCA generated a greater free-fraction recovery than dialysis, suggesting the existence of both diffusible and nondiffusible free-fraction cobalt. The nondiffusible free-fraction cobalt actually may be reversibly bound to plasma protein, only made available as free cobalt after TCA-mediated dissociation from the carrier protein. These results are demonstrated in other work as well (*14*).

Assuming a contamination of 2% ^{56}Co, which seems realistic in clinical practice, the administration of $^{55}CoCl_2$ has to be limited to 18.5 MBq (0.5 mCi) in order to remain in class II studies as defined by the WHO. Accordingly, the maximal dose of ^{57}Co is 11 MBq (0.3 mCi).

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