Dosimetric Optimization of Postproduction Neutron-Activated Erbium-170-Oxide-Enriched Pancreatin

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The feasibility of postproduction neutron activation of an enteric-coated pancreatic enzyme preparation for in vivo gastric emptying studies has been investigated. **Methods:** During production of this multicomponent preparation, small amounts of ^{170}Er-enriched erbium oxide, suitable for neutron activation, were added. **Results:** Postproduction neutron irradiation of the labeled preparation resulted in short-lived (7.5 hr) gamma-emitting ^{171}Er. Various radiocontaminants, however, are produced also. Because of variations in activation yields, half-lives, decay schemes and radiotoxicities, both major and trace constituents were considered for optimization of both dosimetry and the diagnostic measurement. Conditions were optimized for the best ratio of the committed dose equivalent due to ^{171}Er to the total committed dose equivalent. **Conclusion:** The results show that postproduction neutron activation of a ^{170}Er-enriched multicomponent preparation can be performed safely within the guidelines set by the WHO for experiments in humans involving radioactive materials.

Key Words: dosimetry; erbium-170-enriched erbium-oxide; neutron activation; WHO guidelines; pancreatin

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Production of pharmaceutical preparations often involves delicate procedures that determine stability, bioavailability and the controlled release of an active substance. It is difficult to radiolabel an enteric-coated (EC) preparation without significant interference. For a particular clinical study aimed at investigating whether EC pancreatin microspheres pass the pylorus simultaneously with a standardized test meal, a suitable procedure for radiolabeling had to be developed.

EC pancreatin microsphere preparations are used in the treatment of exocrine pancreatic insufficiency. The gelatine capsule, which contains the microspheres, dissolves in the stomach. To protect the enzymes within the EC microspheres from acidic inactivation, enzyme release is pH-dependent and starts in the small intestine when the pH exceeds 5.5. During the gastric emptying studies involving this EC pancreatin microsphere preparation, actual enzyme activities in the small intestine are to be measured simultaneously. The radiolabeling procedure, therefore, must not affect the pH-dependent release, as is likely to happen when the microspheres are radiolabeled after production. Radiolabeling the enzymes themselves was considered unsuitable because it would require long-lived radionuclides and involve handling of radioactivity in an industrial facility.

Thus, the only suitable technique would be postproduction neutron activation of the microspheres. For this, small amounts of a nuclide with a high cross-section for (n, γ) reaction had to be added to the raw material (i.e., pancreatin). The activation product had to be compatible with dual isotope acquisition on conventional scintillation cameras. Preliminary experiments had shown that it was possible to replace part of the filler compound, used to produce the EC pancreatin microspheres, by erbium-oxide. The photon energies of the main activation product ^{171}Er ($t_{1/2}$: 7.5 hr; photon energies: 308, 296, 112 and 124 keV) are compatible with the simultaneous use of a ^{99m}Tc-labeled test meal in a dual-isotope study. Earlier work (unpublished) involving ^{111}In in dual-isotope gastric emptying studies indicated that a dose of 4 MBq of ^{171}Er would be sufficient.

Erbium-171-enriched erbium-oxide has been used to monitor gastrointestinal transit of EC pharmaceuticals such as ibuprofen and erythromycin (*1,2*). These are mono-component preparations. An EC pancreatin microsphere preparation, however, is a complex multi-component preparation which contains many proteins and elements of porcine pancreatic origin. Therefore, neutron activation of the EC pancreatin microspheres will result in other activation products (AP) besides ^{171}Er. The yields depend on the physical properties of all constituents in-

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TABLE 1
Constituents and Contaminants, in a 415-mg EC [^{170}Er]Erbium-Oxide-Enriched Pancreatin Preparation and Potential Dosimetric Impact When Subjected to Neutron Activation

Element†	Presence in ppm w/w‡	Source of data§	Isotope	Daughter	Yield	Dose (ALI)
Na	5880	1	^{23}Na	^{24}Na	400 kBq	0.0089
P	15000	2	^{31}P	^{32}P	16 kBq	0.0019
S	3000	2	^{34}S	^{35}S	650 Bq	<0.0001
K	4380	1	^{41}K	^{42}K	36 kBq	0.0007
Cr	110–364¶	3	^{50}Cr	^{51}Cr	460 Bq	<0.0001
Mn	10	1	^{55}Mn	^{56}Mn	7.5 kBq	<0.0001
Cu	<200	1	^{63}Cu	^{64}Cu	32 kBq	0.0002
As	<0.45	1	^{75}As	^{76}As	59 Bq	<0.0001
Pr	5	4	^{141}Pr	^{142}Pr	1.1 kBq	0.0001
Eu	<0.025	1	^{151}Eu	^{152m}Eu	990 Bq	<0.0001
Tb	25–36¶	3	^{159}Tb	^{160}Tb	300 Bq	<0.0001
Dy	15–43¶	3	^{164}Dy	^{165}Dy	520 kBq	0.0026
Ho	10–15¶	3	^{165}Ho	^{166}Ho	19 kBq	0.0019
Er	<32	3	^{164}Er**	^{165}Er	8.3 kBq	<0.0001
	289	3	^{168}Er**	^{169}Er	990 Bq	<0.0001
	31100	3	^{170}Er**	^{171}Er	4.4 MBq	0.0867
Lu	0.4–25¶	3	^{175}Lu	^{176m}Lu	16 kBq	0.0002

*Thermal neutron flux $5.5 \cdot 10^{16} \cdot m^{-2} \cdot s^{-1}$, irradiation for 4 min and an IAI of 8 hr.

†All natural elements except noble gases were taken into consideration and when possible checked for by INAA. Many elements had a very limited contribution to the patient dose (<0.00005 ALI; <1 μSv each) and are not included in the table.

‡Source of analysis data: 1 = INAA (EC pancreatin microspheres); 2 = Nordmark GmbH (EC pancreatin microspheres); 3 = Campro Scientific (enriched erbium-oxide); and 4 = Worst case estimate.

§Data obtained from INAA, Nordmark GmbH and worst case estimates refer to the presence of elements (ppm w/w) in the EC ^{170}Er-enriched erbium-oxide pancreatin microspheres (without the gelatine capsule). Except for Cr, data obtained from Campro Scientific refers to the presence of isotopes (ppm w/w). The total weight of the EC ^{170}Er-enriched erbium-oxide pancreatin microspheres is 415 mg.

¶Range based on analysis results of two different batches of ^{170}Er enriched erbium-oxide.

**Concentrations corrected for isotopic enrichment.

volved. Most important are the isotopic abundances, the cross-sections for (n, γ) reactions, the decay schemes, as well as the half-lives of the APs formed. Cross-sections and abundances for various elements vary several orders of magnitude, so that large differences in APs are observed. Major constituents of pancreatin such as carbon, oxygen, nitrogen and hydrogen, do not result in measurable APs. Some elements, however, such as sulphur, phosphor and sodium do result in measurable APs. Trace element constituents may lead to significant amounts of APs. Trace contaminants in the enriched erbium-oxide which is not entirely isotopically and chemically pure may also result in additional APs. The dosimetric impact of a radiocontaminant varies with its physical half-life, decay mechanism, decay products, route of exposure, chemical composition and various biological parameters. Hence, its significance cannot be judged from the initial concentrations and isotopic abundances alone. All these factors have a multiplicative effect that may span more than 10 orders of magnitude.

Since common hospital equipment for gamma-spectrometric quality control is not adequate to detect all relevant contaminants, we undertook a more detailed analysis for dosimetric evaluation. Unfortunately, little literature exists that covers the dosimetry of complex activated materials or techniques for optimization of the committed dose equivalent (CDE) in such cases. Our approach was essentially a system analysis (*3*).

MATERIALS AND METHODS

Panzytrat® 20.000 (Nordmark Arzneimittel GmbH, Uetersen, Germany) is a hard gelatine capsule containing about 50 microspheres with a pH-dependent release regulating coat. The microspheres are manufactured by compressing pancreatin obtained from porcine pancreatic glands with auxiliary filler substances. The pH-dependent release regulating coat is applied using an aqueous latex dispersion of polymers based on polyacrylates. Each capsule contains about 240 mg of pure pancreatin, corresponding to circa 20,000 units lipase, circa 18,000 units amylase and circa 1,000 units protease (units according to the European Pharmacopeia). The shelf-life at room temperature is at least 12 mo. For this study, part of the filler compound of a single batch of capsules, each containing 50 EC pancreatin microspheres, was replaced by ^{170}Er-enriched (97.9%) erbium-oxide; 0.3 mg per microsphere. The impurities, as specified by the supplier (Campro Scientific, Veenendaal, The Netherlands), are included in Table 1.

Chemical and Isotopic Composition

The concentrations listed in Table 1 were derived as follows: For the ^{170}Er label, the atomic absorption spectrometry (AAS) data of the supplier have been used. The data on Si, P, S, and Ca concentrations in pancreatin were provided by Nordmark Arzneimittel GmbH. For other elements in the pancreatin, instru-

TABLE 2
Effect of the Interval between Activation and Ingestion (IAI) on Relative Contributions to the Committed Dose Equivalent

IAI (hr)	^{171}Er	^{24}Na	^{32}P	^{42}K	^{165}Dy	^{166}Ho
1	0.797	0.059	0.010	0.005	0.104	0.011
6	0.838	0.075	0.017	0.005	0.039	0.017
8	0.839	0.080	0.020	0.007	0.026	0.019
12	0.828	0.092	0.028	0.008	0.011	0.025
24	0.729	0.124	0.074	0.011	0.001	0.048
48	0.365	0.146	0.320	0.013	0.000	0.117

mental neutron activation analysis (INAA) (*4,5*) was used, supplemented by worst-case estimates for pure beta-emitters and elements for which INAA could only provide upper limit values. From these data, the activities of the various resulting APs were calculated using a computer program developed by the Interfaculty Reactor Institute which is based upon the Neutron Activation Tables by Erdtman (*6*) and accounts for both (n, γ), (n, p) and (n, α) reactions, as well as the actual fluxes of thermal, epithermal and fast neutrons in the irradiation facility. Manual corrections were made in case of isotopic enrichment. Only those elements leading to APs that remained detectable at least 2 hr after irradiation were taken into account.

Neutron Activation

Neutron activation took place at the 2 MW nuclear reactor of the Interfaculty Reactor Institute. Individual capsules were irradiated at a thermal neutron flux density of $5.5 \cdot 10^{16} \cdot m^{-2} \cdot s^{-1}$. The duration of activation was adjusted to obtain 4 MBq ^{171}Er at the time of ingestion. Before actual ingestion, the activated EC pancreatin microspheres were repackaged in a nonirradiated gelatine capsule. The optimal interval between activation and ingestion (IAI) was defined as the interval with the highest ratio of CDE due to ^{171}Er to the total CDE.

Dosimetry

For IAIs ranging from 1 to 48 hr, the ingested activity per radionuclide for unit duration of activation was calculated. Activities were expressed in annual limits on intake (ALIs), as defined in ICRP-61 (*7*). When multiple ALIs were given, the lowest was used. It was always explicitly checked that the chemical form and the route of intake were compatible with the respective underlying assumptions on which the limits in ICRP-30 and ICRP-61 are based (*7,8*). Otherwise, the ingested activity was multiplied accordingly to compensate for such a fact. If a correction in the fraction absorbed from the gastrointestinal tract (F1) seemed prudent, an F1 of 1.0 was assumed and the ALI was decreased accordingly. When no ALI was available, a worst-case value of 100 kBq and an F1 of 1.0 was assumed. The contributions, expressed in ALIs, were summed and multiplied by 0.02 Sv. When an ALI was based on a limiting target organ, no adjustment was made. The CDE thus obtained was multiplied by a safety factor of 1.5 to compensate for all remaining uncertainties. This final value, for the chosen IAI and duration of activation, was reported to the Medical Ethics Committee as the upper limit of the CDE for a male volunteer or patient with a body weight of 75 kg.

For selected constituents, the impact of a tenfold concentration increase on optimum IAI and on total CDE was assessed.

Quality Control

Capsules were activated for 1, 2, 4, 8 and 17 min. Measurements included enzyme activities of lipase, amylase and protease as well as gastric fluid resistance of the enteric coat and the disintegration time of the EC microspheres.

From the yields and gamma energies of the APs, it was calculated whether interference in scintillation camera operation could be expected at the optimal IAI.

RESULTS

Chemical and Isotopic Composition

Table 1 lists the concentrations per element on a per weight basis, the resulting APs and their dosimetric impact for a 4-min neutron irradiation and an IAI of 8 hr. Only elements and isotopes of dosimetric relevance are included (>1 μSv). For some elements and isotopes, the results from two different batches of ^{170}Er-enriched erbium-oxide are given to show the significant variation for the contaminants.

Dosimetry

The effects of varying the IAI interval (1–48 hr) on the contribution of ^{171}Er and the most important APs to the CDE are given in Table 2. The optimal IAI is in the range of 6–8 hr, where APs contribute less than 20% to the total CDE. At the optimal IAI (8 hr), the total CDE for all radionuclides combined (resulting from neutron irradiation of 415 mg of ^{170}Er-enriched pancreatin microspheres for 4 min) including all safety factors, does not exceed 0.75 mSv per MBq of ingested ^{171}Er. Individual contributions of radionuclides to the patient dose are listed in Table 1.

For various isotopes, the effect of a tenfold increase in their concentration on the IAI and the CDE was assessed. For ^{32}P, the IAI was not affected, but the CDE increased by 2%. For both ^{24}Na and ^{166}Ho, the optimum IAI decreased by 2 hr, whereas the CDE increased 7% and 10%, respectively. For ^{165}Dy, the optimal IAI increased by 1.5 hr at an increase of 2% of the CDE. Any deviation from the optimal IAI results in a further increase of the CDE.

Quality Control

After 1, 2, 4, 8 and 17 min of neutron irradiation, lipase activity amounted to 20,400, 18,500, 17,200, 13,700 and 9500 U/capsule, respectively. Amylase activity was 18,100, 17,200, 15,500, 13,700 and 9900 U/capsule. Protease activity amounted to 1170, 1130, 1040, 970 and 780 U/capsule. After 4 min of neutron irradiation, lipase activity was 86% of the nominal value, amylase activity 86% and protease activity 100%. Even after 17 min of neutron irradiation, gastric fluid resistance of the microspheres was not af-

fected and the disintegration time of the EC microspheres decreased from 7.2 to 6.1 min.

It was experimentally confirmed (results not shown), that the number of high-energy photons from other APs was small and could be corrected for with our software, which incorporates down-scatter correction and background subtraction. The total activity of ^{99m}Tc for the test meal largely exceeds any contribution from either bremsstrahlung or the scattered photons from ^{171}Er and other APs.

DISCUSSION

Chemical and Isotopic Composition

The contribution of APs to the CDE depends on the chemical and isotopic purity of the ^{170}Er oxide, the chemical composition of the unlabeled pancreatin preparation and the IAI.

Erbium-oxide, isotopically enriched to 97.9%, was used to increase the ratio of ^{171}Er activity to other APs more than sixfold. Despite the enrichment, however, 5400 ppm of other lanthanides were present in the enriched material, contributing 4.5% to the CDE at the optimal IAI of 8 hr. Thus, enriched materials must be carefully selected. Isotopic enrichment must also be assumed for the contaminants in the enriched radiolabel. The APs formed from constituents (i.e., sodium, potassium, sulphur and phosphorus) of the pharmaceutical preparations itself, contributed for 11% to the CDE at the optimal IAI.

The dosimetric optimization requires exact knowledge on the presence of all constituents, including trace elements. Some of these trace elements may be important because of their large cross-section and/or low ALI-value of the resulting AP (ALI-values may differ up to five decades). The advantage of INAA is that elements with large neutron cross-sections, which contribute most to APs, can be measured with good sensitivity. Some elements, however, lead to pure beta-emitting radionuclides only and must be measured separately (e.g., phosphor and sulphur).

Dosimetry

Hardly any data are available on the biodistribution of lanthanides in humans. Scant data from rodent studies are inadequate for the MIRD methodology (*7*). ICRP 61 tables for erbium-oxide are based upon the biodistribution of cerium-oxide. For our purposes this was not critical because the amount of uptake from the gastrointestinal tract due to the short half-life of ^{171}Er and most lanthanide contaminants (present as Ln_2O_3) compared to the gastrointestinal transit time hardly affects dosimetry.

For a dosimetric evaluation of radiocontaminants, additional data are required on the chemical form of the contaminant and on the metabolic status of the patient. These data should be cross-checked with the assumptions on which the ICRP 30 and ICRP 61 tables are based. The various assumptions made (see Methods) tend to overestimate the actual patient dose. One may consider our use of ICRP 61 data beyond the intended scope of that document.

TABLE 3
Weight Limits for Naturally Occurring Elements Leading to a Maximum Committed Dose Equivalent of 1 μSv per Element in Case of Oral Intake*

Weight limit (mg)	Elements†
>1000	H, Li, Be, B, C, N, O, F, V, Nb, Rh, Tm, Pb
>100	Mg, Al, Tl, I
>10	Si, Ca, Fe, Tl
>1	S, Cl, Cr, Ni, Ge, Se, Sr, Zr, Ru, Ba, Bi
>0.1	P, K, Zn, Rb, Mb, Ag, Cd, Sn, Ce, Nd, Pt
>0.01	Na, Sc, Co, Cu, Cs, Eu, Gd, Tb, Er, Hf, Ta, Os
>0.001	Mn, Ga, As, Br, Y, Hg, Pd, Sb, Te, La, Yb, Lu, W
<0.001	In, Pr, Sm, Dy, Ho, Re, Ir, Au

*Assumptions on which the table is based: use in healthy volunteers, single dose, thermal neutrons $5.5 \cdot 10^{16} \cdot m^{-2} \cdot s^{-1}$, epithermal neutrons $0.1 \cdot 10^{16} \cdot m^{-2} \cdot s^{-1}$, fast neutrons $0.37 \cdot 10^{16} \cdot m^{-2} \cdot s^{-1}$, activation time of 4 min, interval between activation and ingestion: 8 hr.

†Biodistribution and chemical form similar to that on which the tables of ICRP-61 are based. No further safety factors were applied.

However, given the data available or obtainable without additional experiments in humans and the use of safety factors and worst case assumptions, this approach is the best available at present. When nonstochastic effects are highly unlikely, the effects of the various radionuclides, despite their different biodistribution, are additive (*7,8*).

It proved practical to evaluate the dosimetric impact of contaminants by expressing their contributions as ALIs, as defined in the ICRP 61. Expressing the ingested activity per unit activation duration in ALIs as a function of the interval between activation and ingestion, leads to an optimal interval for which the dose is as near as possible to the total CDE due to imaging photons. In Table 1, all elements except the noble gasses have been taken into account. Elements that are not listed showed only a very limited contribution to the patient dose (<0.00005 ALI = <1 μSv per element). To exemplify the impact of mass, Table 3 lists the mass limits that lead to a contribution of 0.1–1 μSv per element to the CDE for all stable elements, except the noble gases. Isotopically enriched tracers must always be considered separately. The CDE limit of 1 μSv per element was chosen so that individual elements would contribute less than 0.1% to the total CDE in case of typical imaging doses. This is in accordance with the approach in ICRP-30 (*7*).

Quality Control

Neutron irradiation may affect the properties of a pharmaceutical preparation. Our results show a clear dose-effect relation on enzyme activities, but not on gastric juice resistance or disintegration time of the microspheres. For an activation duration of 4 min, the effects of neutron

irradiation were acceptable, and allowed simultaneous in vivo measurements of small intestinal lipase and protease activities during the gastric emptying studies.

Radiocontaminants may interfere with scintillation camera operation and image quality, i.e., septal penetration of the collimator. Due to the different half-lives, the effects of radiocontaminants vary in time. Moreover, the contribution to CDE and interference with camera operation correlate poorly and must therefore be assessed separately. The significant effect APs have on image quality also has to be taken into account. In our case, the IAI could be solely based upon dosimetric considerations.

To guarantee a constant elemental composition for all capsules to be used, the labeled product should be prepared as a single batch. The elemental analysis needs only to be performed once for each batch. Individual capsules may be neutron activated on demand, during any time within the shelflife of the pharmaceutical preparation. Shortly before actual ingestion of the irradiated EC pancreatin microspheres, we obtained a gamma spectrum ranging from 10 keV to 1.5 MeV from each freshly activated capsule, using a shielded and calibrated Ge-Li detector system and multichannel analyzer. This spectrum is compared with a reference spectrum to verify dose.

CONCLUSION

The purpose of this investigation was to establish whether postproduction neutron activation of isotopically enriched multicomponent pharmaceutical preparations for use in human gastric emptying studies is feasible. The results show that such studies can be performed safely, despite various radiocontaminants, within the guidelines set by the WHO for experiments in volunteers involving radioactive materials.

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