Clinical applications of Cobalt-radionuclides in neuro-imaging

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4.2 Summary

This thesis describes the clinical applicability of the divalent unchelated radionuclide 55-Cobalt (Co) as a diagnostic tracer using positron emission tomography (PET). Dosimetry, pharmacokinetics, diagnostic effectiveness and clinical relevance in distinct neurological diseases were assessed using correlation with clinical scores and image-fusion with structural imaging. The experimental rationale of Co is based on the assumed mimicry of Calcium (Ca), thus visualising Ca-related neuronal degeneration and inflammation in brain damage.

Chapter 1: Scope of the thesis

The rationale of the studies described in this thesis, is based on theoretical considerations (chapter 2) and translated into clinical pilot studies (chapter 3). The actual results of these pilot studies are critically discussed (chapter 4).

Chapter 2: General introduction

A historical review of the use of Co as a haematopoetic agent and beer-additive is provided with emphasis on its many adverse side reactions. It is concluded that Co in pharmacological concentrations is a marked cytotoxic and cardiotoxic compound (2.1). The strong in vitro and the weak in vivo evidence of Co-deposition reflecting Ca-accumulation is discussed. Uptake-experiments in neurons, glial cells, and leukocytes, reveal both similarities and differences in the comparison of Co and Ca. Transport of both Co and Ca is competitive and based on receptor-operated membrane Ca-channels. Determination of the actual Co-uptake mechanism in clinical practice is notoriously difficult and may consist of both an intra- and an extravascular contribution. The intravascular Co-deposition is determined by bloodflow (neocapillarisation; luxury perfusion) and bloodvolume (secondary haemorrhage; venous bloodpool). The extravascular contribution comprises gating through receptor-operated Ca-channels, deposition of (protein-bound) Co via a disrupted blood brain barrier (BBB) and infiltration of Co-labelled leukocytes. Both types of contribution are time-dependent and separate mechanisms may coincide. The net result is relatively slow Co-uptake without wash-out, the ability to penetrate intact BBB, uptake in inflamed and/or decaying tissue and minimal Co-uptake in normal brain (2.2). The plasma-profile of Co consists of a soluble free fraction (about 10% of the total plasma Co), a fraction complexed to proteins (both reversibly [Co²⁺-N] and irreversibly [Co²⁺-S]
attached) and cell-bound Co (mainly leukocytes). The $^{60}$Co effective radiation dose (ED) is 0.22 mSv MBq$^{-1}$ (8.0 mSv mCi$^{-1}$); the $^{59}$Co ED is 0.34 mSv MBq$^{-1}$ (12.4 mSv mCi$^{-1}$) (2.2). In contrast to other widely used unchelated tracer such as (Gallium) $^{67}$Ga, (Rubidium) $^{82}$Rb and (Thallium) $^{201}$Tl, Co demonstrates only a delayed signal (ca 6 hours post-administration), produces a low background and shows uptake in cell-decay and inflammation. Typically, Co (ir)reversibly binds to liver proteins (enzymes?) providing a reservoir, possibly accounting for a steady plasma-Co concentration, for at least 72 hours (2.2).

**Multiple Sclerosis** (MS) is an auto-immune central nervous system (CNS) inflammation resulting in multifocal demyelination and axonal loss. MS can demonstrate different courses of disease with each course having its typical contribution of inflammation and cell-decay. Severity of illness can be expressed in clinical scales such as Kurtzke’s Expanded Disability Status Scale (EDSS) and Scripp’s Neurological Rating Scale (NRS) (2.3). The CNS-confined T-lymphocytes, activated in the peripheral blood, mediate the inflammatory process, resulting in waxing and waning of lesions. The cytokine γ-interferon (γIFN) activates Ca-influx in “pre-activated” T-lymphocytes, which in turn start to proliferate and infiltrate the CNS. Apart from Co entering decaying neurons, these γIFN activated T-lymphocytes may accumulate Co and thus account for the inflammatory delivery-component of Co-PET in MS (2.3). Magnetic Resonance Imaging (MRI) is the gold standard in neuro-imaging of MS. However, the lack of association between the clinical course of MS and MRI-findings has been a major concern (the clinical-radiological paradox). Due to difficulties in measuring clinical outcome (“primary outcome measure”) in MS and the lack of specificity of MRI as a surrogate outcome measure (“secondary outcome measure”), there is a need for alternative (complementary) CNS-imaging techniques (2.3). Image-fusion of Co-PET and MRI using an appropriate Statistical Parametric Mapping (SPM) software-package may fill the gap and allow less extensive and costly therapy-evaluation and patient-stratification (2.3).

**Cerebral infarction** (stroke) is a multi-factorial disease classified by mechanism and duration of ischemia, vascular anatomy and residual clinical deficit. Transition from ischemia to infarction involves an “ischemic cascade” with Ca fulfilling a central role. Any stroke therapy must be started within 3-6 hours post-stroke (the ‘therapeutic window’) (2.4). Computed Tomography (CT) and MRI are the gold standard for structural imaging. Additional - more recent - techniques are diffusion MRI and MR Spectroscopy (MRS). X-ray techniques, such as SPECT can demonstrate and thus predicting (to a certain degree) damage are the most crucial step in the mechanical impact): structural damage (SBD), which is related to primary brain tumour grade, and MRI are the gold standard for predicting value in TBI; and secondary outcome measure) and SPECT are of great importance, tumour grade, oedema, differentiation between normal tissue and tumour etc. (2.6).

**Chapter 3: Original Research**

Co-PET was studied in two sets of patients in combination with MRI. Co-PET was performed on admission and Co-PET was performed on admission on two sets of patients (and 7 control patients in each MS-ground) and MRI (Kurtzke’s EDSS and MRI) confirmed the significant
Spectroscopy (MRS). Angiography can be performed using conventional X-ray techniques, spiral CT or MR Angiography (MRA) (2.4). PET and SPECT can demonstrate flow- and metabolism-related aberrations in stroke, thus predicting (to a certain extent) functional recovery (2.4).

**Traumatic Brain Injury (TBI)** can be classified by lesion pattern, time course, and mechanism of injury. Diffuse axonal injury and ischemic brain damage are the most common mechanisms of injury (apart from the primary mechanical impact): secondary brain damage (SBD) (2.5). Ca fulfills a central role in SBD, which is both a neurochemical and a clinical phenomenon. CT and MRI are the gold standard in TBI-imaging. Both PET and SPECT have predictive value in TBI. However, SPECT may be more applicable than PET considering the logistical problems and the urgency of pathology (2.5).

**Primary brain tumours** are classified by cell type, malignancy and clinical prognosis. Clinical features vary depending on location, cell type and tumour grade. Both CT and MRI are of value, but do not differentiate tumour from oedema or distinguish tumour response from tumour progression. More recent techniques include MRS and optical imaging-modalities. Both PET and SPECT are of great value in providing additional information towards tumour grade, oedema versus tumour, radiation effect versus recurrent tumour etc. (2.6).

**Chapter 3 : Original Reprints**

**Co-PET was studied:**

(3.1; 3.2) : in two small series of middle-cerebral-artery (mca) stroke-patients in combination with CT and/or MRI using the Orgogozo mca-stroke scale (on admission and discharge). Since the time interval between stroke-onset and Co-PET was highly variable (0-14 days), the actual (time-dependent) mechanism of Co-deposition will also vary considerably. Apart from the small series studied, this profound uncertainty about the interpretation of results may explain our paradoxical results. Thus, Co-PET using unchelated Co may not be an ideal tool for stroke-imaging.

(3.3; 3.4) : both in a small series of 7 secondary progressive MS (SP-MS) patients (and 7 controls) and in a series of 32 MS-patients comprising 8 patients in each MS-course (and 8 controls). Image fusion of PET (foreground) and MRI (background) was used (SPM-95 software package); Kurtzke’s EDSS and Scripp’s NRS were used as clinical impairment scales. Most MRI-lesions could be retrieved as Co-PET lesions. Both studies confirmed the significant correlation between the mean number of lesions on Co-
PET on the one hand and the progression rate (ΔEDSS / year) of disease on the other. Inter-observer correlation was significant in all courses except the RR-course. The co-registration technique seems to be a fundamental trade-off between sensitivity and specificity.

(3.5) : in 5 TBI patients demonstrating focal Co-uptake in good correlation with EEG-findings and neuropsychological testing. Sensitivity extended beyond the limitations of structural imaging (CT; MRI).

(3.6) : in 3 primary brain tumours demonstrating rim-enhancing uptake around a necrotic tumour core. Histopathological diagnosis was obtained by biopsy or resection. Viable tumour-tissue did not show Co-accumulation; uptake indices in (probably) decaying tissue varied between 2.6 and 5.3. MRI and/or CT, used as structural imaging modality, could not clearly delineate either oedema or necrosis from tumour issue.

(3.7) : pharmacokinetics and dosimetry of 58Co and 59Co were studied in rats and 3 healthy volunteers. Based on pharmacokinetic data, radiation dose calculations according to the MIRDOS 3 system are presented. The liver and the bladder retain the highest fractions of 58Co, respectively 50% and 40% of the administered dose. The free fraction 58Co in the human plasma is at maximum 12%. The volume of the central compartment (2.8 litres) is in the same order of magnitude as the calculated plasma volume (3.0 litres). The 58Co effective radiation dose (ED) is 0.22 mSv MBq⁻¹ (8.0 mSv mCi⁻¹) with a half-life of 18.5 hours (biological half-life 37.6 hours); the 59Co ED is 0.34 mSv MBq⁻¹ (12.4 mSv mCi⁻¹) with a half-life of 270 days (biological half-life 37.6 hours).

Chapter 4: General Discussion

In Concluding remarks and future perspectives the respective contribution of neuronal decay and inflammation to net Co-deposition is discussed (4.1). Both Co-PET and Co-SPECT may have great clinical potential in nuclear neuro-imaging. Apart from extending the present studies into larger patient-series (MS, TBI, primary brain tumours) and entering new areas of interest (Dementia of the Alzheimer Type; Acute Myocardial Infarction), the quest for Co-labelled inflammatory proteins and leukocytes may open an additional field of research (4.1).

This research-project was supported by a grant (SSN 22.2741) from the Dutch Technology Foundation (STW) and a grant (93-152 MS) from the Foundation for support of MS Research (Stichting Vrienden MS Reseach).