LATE EFFECTS OF THOROTRAST AMONG DANISH PATIENTS 1932-1947

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Project details

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Objective

In 1929 Radt (Berlin) and Oka (Tokyo) introduced a stabilized 25% colloidal solution of thorium dioxide as a radiodiagnostic contrast medium which was sold under the trade name Thorotrast. The predominant form of application was an intravascular injection, especially for cerebral angiography. After intravascular injection the ThO2 aggregates accumulate in the reticuloendothelial system (RES) and are stored for life.

From the data on the 232Thorium distribution in the tissue and the activity ratios combined with information about the various types of radiation, the average energy per decay of each radionuclide and the cell absorption of alpha-particles in ThO2 aggregates, Kaul and Noffz calculated mean values for the annual radiation dose of the organs of the RES. A mean intravascular injection of 25 ml Thorotrast in a 70 kg person causes the following absorbed dose rates: liver 25 cGy/year; spleen 70 cGy/year; bone marrow 9 cGy/year; endothelial layer in bone 16 cGy/year; kidneys 0.4 cGy/year. The radiation dose in the lung tissue is mainly caused by the daughter product 220Rn which is exhaled by the breath.

The objective of the German Thorotrast study was:
- to trace the largest possible number of Thorotrast patients who had been given intravascular injection;
- to determine the thorium dioxide quantities incorporated;
- to compare the health and the fate of Thorotrast patients with those of a control group;
- to relate long term effects of Thorotrast found to the radiation dose in the depository organs.

Apart from answering these scientific questions, it was intended to provide a comprehensive treatment for these patients and to advise the physicians as well as the patients themselves.

Objectives for 1990 and 1991

The working programme will be continued according to the recommendations of the coordinating committee:
- regular correspondence with about 600 patients of the Thorotrast and control group as well with the respective family physicians;
- outpatient reexaminations of Thorotrast carriers and patients of the control group at two years intervals;
- computer suitable registration of examination data and medical reports of the family doctors as well as the treating hospitals;
- controlling of the stored data and preparation of final statistical evaluation.

Research has been carried out in order to describe and analyse by epidemiological methods, the potential long term health effects of intraarterial exposure to Thorotrast in Danish patients injected for cerebral angiography during 1935 to 1947. A follow up study was set up in 1949 but has been inactive. The present study reidentified all persons, reverified Thorotrast exposure and comprehensively followed up all persons with regard to vital status, cancer incidence, cause of death, and incidence of nonmalignant diseases and related the incidences to that of the general population and to Thorotrast dose and demographic variables.
Information regarding 1095 persons was found in the original material. 96 persons were excluded mostly because Thorotrast exposure could not be verified and was considered to be less possible (56 persons). Thus, the study population consisted of 999 historical prospectively registered Danish residents with Thorotrast exposure for cerebral angiography with fully identified vital status and information of date of Thorotrast injection and volume of Thorotrast injected.

The overall sex and site specific cancer incidence with relative risks has been listed. In general the cohort experienced an elevated cancer risk compared to the Danish population. The high incidence of cancer of the central nervous system was remarkable. This was due to an extremely high incidence in the years immediately following the Thorotrast exposure and is a reflection of brain tumour often having caused symptoms due to which the cerebral angiography was performed.

Also notable was the extremely high incidence of liver cancer. This has been described earlier in other trials. In contrast to the German study, there was a significantly increased risk of lung cancer among males in the Danish study and a similar, however, statistically insignificant, increased risk in females.

Other sites which presented a higher than expected incidence was breast (relative risk (RR) 1.80), ovary (RR 2.44), other skin among females (RR 2.41), eye among females (RR 15.2), metastases and other unspecified sites among both females and males, multiple melanoma among females (RR 11.0) and leukaemia in men and women (RR 10.6). Finally 3 cases of cancer of peritoneum, (2 mesotheliomas) appeared among men (RR 18.9). Data are being further analysed and related to age at injection, injected volume and so on.

Thorotrast specific diseases (liver cancer, cirrhosis or leukaemias) we see similar results in dose-rate dependent life phenomenon depends on the amount of Thorotrast injected. Excluding from the analysis those patients who died from

During the past years there has been a constant trend for Thorotrast patients to die earlier compared to controls. This was due to an extremely high incidence in the years immediately following the Thorotrast exposure and is a reflection of brain tumour often having caused symptoms due to which the cerebral angiography was performed.

Also notable was the extremely high incidence of liver cancer. This has been described earlier in other trials. In contrast to the German trial there was no tendency to a higher incidence of liver cancer among men than in women. Likewise, in contrast to the German study, there was a significantly increased risk of lung cancer among males in the Danish study and a similar, however, statistically insignificant, increased risk in females.

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A study has been made of patients (999) injected with the X-ray contrast medium thorotrast (thorium dioxide) during the years 1932 to 1947 in Denmark, in order to determine the long term risk of exposure to low dose alpha radiation. Cancer related mortality was highly increased and the standardised mortality ratio (SMR) was related to the injected amount of thorotrast. SMR for all other categories of cause of death was also increased and related thorotrast dose. The standardised incidence ratio (SIR) for cancer at all sites except brain and central nervous system was significantly increased (cumulative risk after 50 years 86%) mainly due to high risks of liver cancer and leukaemia. Liver tumours induced by alpha radiation are being screened for p53 mutations, which are implicated in carcinogenesis. Anaplastic small cell lung cancer accounted for 50% of lung tumours where normally such tumours would account for 25%. This is interesting in the light of findings that underground miners exposed to radon have increased risk of these tumours. The results from the study indicate that alpha radiation is possibly a powerful carcinogen in man.

Patients and methods of examination

Most of our patients were injected intravascularly with Thorotrast in the period between 1937 and 1947. The names and addresses of more than 5000 patients who had cerebral arteriography (70%) or arteriography of the upper and lower limbs (30%) with Thorotrast were obtained from the records of different hospitals in West Germany. In none of our patients was Thorotrast injected for the actual detection of liver disease.

A pseudorandomized non-Thorotrast control group was set up. It was made up of persons who had been inpatients at the same hospital and in the same year as the Thorotrast patients. To set up the roster, only patients with a surname starting with the letter B were used. The conditions for which either the Thorotrast patients or the controls were admitted to hospital was not considered in the selection. The control group and the group of Thorotrast patients were only matched for age and sex of the patients. In 1968 when the study was started a large number of the Thorotrast patients had already died. The causes of the death of those patients were clarified by hospital records, postmortem examinations, etc.. Patients who died in the first three years after Thorotrast injection were excluded from the evaluation to minimize the influence of the underlying diseases. Excluding the patients who died within the first three years, patients who are not traceable and those not responding, the German Thorotrast study comprises 2326 Thorotrast patients and 1890 control patients of which 2151 Thorotrast patients and 1493 controls have died up to 1990.

Organs with extremely low doses from the locally incorporated Thorotrast are reached, however, by the daughter product radon which is distributed by the blood stream. It is of high interest to calculate the cumulative dose for those organs which show no cancer excess rate.

During the past years there has been a constant trend for Thorotrast patients to die earlier compared to controls. This phenomenon depends on the amount of Thorotrast injected. Excluding from the analysis those patients who died from Thorotrast specific diseases (liver cancer, cirrhosis or leukaemias) we see similar results in dose-rate dependent life shortening. So it is most probable that there is a Thorotrast dependent influence on age at death.

Coordinator

DANISH CANCER SOCIETY
INSTITUTE OF CANCER EPIDEMIOLOGY ROSENVÆNGETS HOVEDVEJ 35
2100 KOBENHAVN
Denmark

Administrative contact: JENSEN
Tel.: +45-1-268866