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Distribution Pattern of Radioactive Labelled Lipiodol-UF® Following Intralymphatic Application for Therapy

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Summary

Endolymphatic radiotherapy with 4 mCi ^{32}P tri-n-octylphosphate and 1 mCi ^{131}I triolein LIPIODOL UF has been performed in 75 patients suffering from malignant melanoma of the lower extremity. On the average, 13.3% of the radioactive substance remains in the syringes and connecting tubes. In most patients the radioactive material available for therapeutic irradiation is further reduced due to contamination of operation sheets and swabs (mean: 15.3%). There is, however, still sufficient radioactivity remaining for effective internal irradiation of the lymph nodes. The average radiation dose absorbed by the lymphatic tissue is 90.998 rad. The method is limited by the hazard of radiation damage to the lungs. Almost 80% of these patients had detectable concentrations of radioactivity in the lung fields. The average radiation dose was found to be 299 rad. So far radiation induced fibrosis has not been observed in this series.

For calculation of the radiation dosage in endolymphatic radiotherapy (ELRT) one needs to know (1) the distribution pattern of the applied radioactive substances, (2) the weight of the lymphatic tissue reached by the labelled compounds, and (3) the amount of radioactive material remaining in the injecting system.

In a series of 75 patients treated by intralymphatic administration of ^{32}P tri-n-octyl-phosphate and ^{131}I triolein labelled LIPIODOL-UF® the following measurements were carried out:

- measurement of the radioactive substances as shipped from the manufacturer immediately prior to injection,
- measurement of the radioactivity remaining in syringes, connecting tubes and needles after completion of the intralymphatic application,
- measurement of the radioactivity spilled unto operation sheets and swabs during cannulation and connecting procedures, and
- determination of the distribution pattern of the applied radioactive substances by means of whole body profile scanning.

The radioactive substances are delivered by the manufacturer* in special lead shielded syringes ready for use (2, 6). Each syringe is filled with 3.5 ml radioactive LIPIODOL-UF® containing 2 mCi ^{32}P tri-n-octyl-phosphate and 0.5 mCi ^{131}I triolein for lower extremity application. Radioactive phosphorus emitting a pure beta radiation serves as therapeutic agent while the gamma radiation of ^{131}I is used for external counting and imaging.

The two labelled compounds are always kept separately and measured before being loaded into the syringes. Experiments at the Radiochemical Centre Amersham and at the German Federal Institute for Physics and Technology (Braunschweig) have in fact shown that it is impossible to obtain exact measurements after the two radionuclides have been mixed together. The beta radiation emitted by the decay of ^{32}P cannot be differentiated from the beta radiation originating

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from the decay of ^{131} I. The contrast medium LIPIODOL-UF® has an interferring effect on the measurements. Due to its very high iodine content a strong internal absorption arises but at the same time "Bremsstrahlung" occurs. The amount of inactive LIPIODOL-UF® required for dilution varies according to the specific activity of the two radionuclides. Therefore, internal absorption and "Bremsstrahlung" can vary a great deal.

At the manufacturer ^{131} I radiation measurements are carried out by means of a calibrated ionisation chamber and the ^{32}P measurements are done in a scintillation well counter utilizing its "Bremsstrahlung".

Results

Endolymphatic radionuclide therapy (ELRT) was carried out in 75 patients suffering from malignant melanoma of the lower extremity following wide excision of the primary tumor (2, 6). Bilateral injection of the radioactive labelled contrast medium was performed in 67 patients, unilateral application in 8 patients. In the latter group bilateral injection was also intented but could not be achieved for technical reasons. Thus, the attempt was made to treat only the diseased extremity using occasionally larger volumes of the radioactive solution.

1. Measurement of the radioactive substances immediately prior to injection:

Control measurements of the ^{131} I gamma radiation prior to injection revealed only very slight deviations from the specifications given by the manufacturer. Therefore, the precalibrated doses – 2 mCi ^{32}P + 0.5 mCi ^{131} I per syringe – could be accepted as baseline values for the following calculations.

2. Measurement of the radioactivity remaining in syringes, connecting tubes and needles after completion of the intralymphatic injection:

Following bilateral injection of the radioactive substance 0.53 ± 0.3 mCi ^{32}P tri-n-octyl-phosphate, i.e. 13.3% of the initial dose, was shown to remain in syringes etc. In seven cases, where for technical reasons the radioactive compound could be administered only unilaterally the fraction of radioactivity remaining in the injection system was even higher: 0.87 ± 0.57 mCi (= 21.7% of the initial dose, Table 1).

The difference is accounted for by the fact that the total volume intended for bilateral injection (7.0 ml) was not used on one extremity only in order to keep the radiation dose to the lungs as low as possible.

Table 1 Radioactive material remaining in syringes, connecting tubes etc. or spilled unto operation sheets, swabs etc.

	Bilateral injection N = 67	Percentage initial dose	Unilateral application N = 7	Percentage initial dose
Syringes etc.	0.53 ± 0.30 mCi	13.3	0.87 ± 0.57 mCi	21.7
Operation sheets etc.	0.61 ± 0.53 mCi	15.3	0.86 ± 0.92 mCi	21.5
Total	1.14	28.8	1.73	43.2

3. Measurement of the radioactivity spilled unto operation sheets and swabs during cannulation and connecting procedures:

The radioactive contamination of operation sheets and swabs results mainly from leakage at the different connections of the injection system and to a lesser extent from leakage around the cannula. Only 5 out of 67 patients with bilateral application of ^{32}P/^{131} I labelled LIPIODOL did not reveal any radioactive contamination. The average amount spilled unto operation sheets and swabs was 0.61 ± 0.53 mCi which is 15.3% of the initial dose (Table 1).

Once again, the corresponding value in patients with unilateral application was higher: 0.86 ± 0.92 mCi or 21.5% of the initial dose. This figure reflects the technical problems in that group of patients.

4. Determination of the distribution pattern of the applied radioactive substance by means of whole body profile scanning:

The main portion of the injected radioactive substance is stored in subdiaphragmatic lymph nodes. As in diagnostic lymphography occasionally a few lymph nodes above the diaphragm are visualized. In 67 bilaterally treated patients on the average 76.8 ± 16.0% of the injected radioactive compound was stored in the lymph nodes. In 8 patients with unilateral application 64.2 ± 22.5% were shown to be in the lymphatic system.

For dosimetric purposes the weight (W) of the lymphatic tissue reached by the radioactive substance has to be assessed. We utilized a previous reported method which requires volume calculations of every individual opacified lymph node (3–5). In this method the lymph nodes are assumed to be essentially elliptical, thus the volume formula of rotation ellipsoids can be applied. Correction is made for geometric magnification (Focus-Film-Distance = 110 cm, Object-Film-Distance = 17 cm):

$$W = \frac{4}{3} \pi \times \frac{L}{2} \times \frac{(110 - 17)}{110} \times \left(\frac{B}{2}\right)^2 \times \left(\frac{110 - 17}{110}\right)^2$$

$$W = 0.312 \times L \times (B)^2$$

where:

W = the volume of a single lymph node
L = its length in cm taken from an a.p. radiograph (FFD – 110 cm)
B = its breadth in cm taken from an a.p. radiograph (FFD – 110 cm)

The effective half-life of ^{32}P tri-n-octyl-phosphate in lymph nodes was taken to be the physical half-life of 14.3 days (3–5).

The calculated radiation dose absorbed by the lymph nodes varied between 8.360 and 236.908 rad with a mean value of 90.998 ± 40.000 rad (Table 3).

From the known amount of actually injected radioactive labelled LIPIODOL and the assessed weight of the lymphatic tissue one can derive the storage capacity of an individual patients lymph system. On the average 0.22 ml contrast medium were stored per gram of lymphatic tissue (range: 0.08 – 0.38 ml/g lymphatic tissue).

There was neither a statistically significant correlation between the storage capacity of normal structured lymph nodes and the age of the patient, nor between the weight of the opacified lymph nodes and the patients age (Fig. 1). Merely the number of opacified lymph nodes and the patients age showed a statistically significant inverse relationship (Fig. 2).

In spite of the low total volume of 7 ml for bilateral injection, spillover of some of the intralymphatically injected radioactive compound via thoracic duct into the lungs often occurs (1, 6). Only 12 out of 67 patients with bilateral application did not reveal radioactivity in the lungs. On the average 19.6% of the injected material was registered over the lung fields (Table 2).

Assuming a standard lung weight of 1000 g and an effective half-life for ^{32}P of 10 days, the average radiation dose absorbed by the lungs is 299 ± 232 rad in patients with bilateral injection (3–5). Similar values were obtained in patients with unilateral application (Table 3).

Extravasations along the course of the peripheral lymphatic vessels are usually welcome, and may provide prophylactic irradiation of metastases in the lymph vessels (6). A total of 16 patients demonstrated such extravasations (Table 2). None of these patients revealed local radiation damage.

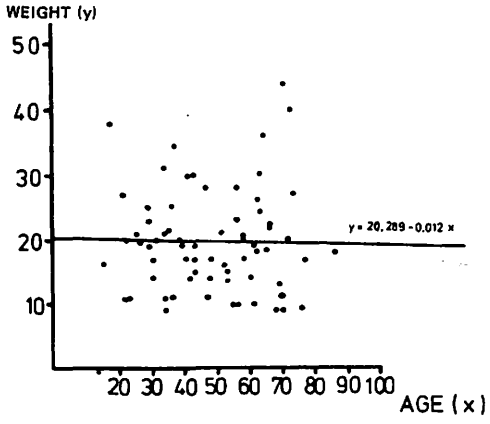

Fig. 1 Correlation between age and assessed lymph node weight (y = 20.289 – 0.012x)

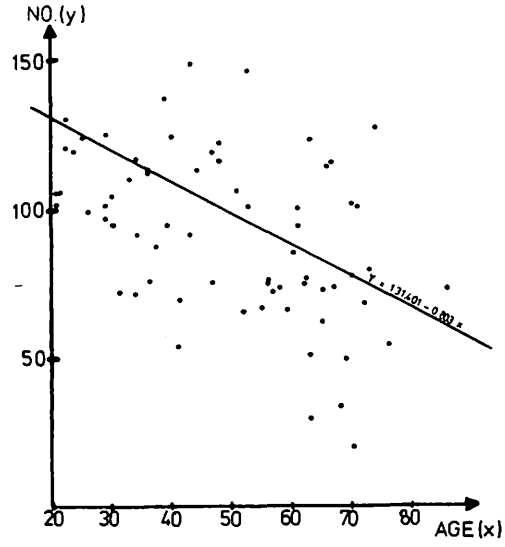

Fig. 2 Correlation between age and number of opacified lymph nodes (y = 131.401 – 0.03x)

Table 2 Distribution pattern of intralymphatically administered radioactive ^{32}P-tri-n-octyl-phosphate

	N	Bilateral application	N	Unilateral application
Lymph nodes	67	76.3 ± 16.0% Range: 33–100	8	64.2 ± 22.5% Range: 19–93
Lungs	67	19.6 ± 14.3% Range: 0–53	8	28.5 ± 21.4% Range: 0–69
Extravasation	13	16.3 ± 16.0% Range: 1–60	3	20.0 ± 18.4% Range: 7–41

Table 3 Radiation absorbed doses (rad)

	N	Bilateral application	N	Unilateral application
Lymph nodes	67	90.998 ± 40.000 Range: 8.360–236.908	8	94.616 ± 51.400 Range: 33.000–157.694
Lungs	67	299 ± 232 Range: 0–872	8	289 ± 312 Range: 0–959

Traces of ^{131}I were found in the thyroid gland in 6 out of 75 patients. The concentration of radioactivity in blood and urine has not been studied.

Discussion

The above reported data are limited in many ways: the method of assessing lymph node weights might not be accurate enough, the assumption of a standard lung weight of 1000 g is probably to rigid and even the method of profile scanning instead of using a whole body counter gives rise to criticism. Nevertheless, a number of conclusions can be drawn which are of utmost importance for everybody performing endolymphatic therapy with radionuclides.

Approximately 1/3 of the total radioactivity remains extracorporal. It can be regularly found in

syringes and connecting tubes, whereas operation sheets and swabs do not always have to be contaminated.

Of the radioactive substance actually injected only about 70% reaches it destination – the lymph nodes. The great variations of the individual values can be attributed to the differences in weight and storage capacity of the lymph nodes. This factor of uncertainty has to be accepted as the treatment procedure would be greatly complicated if the weight of the lymph nodes had to be determined before endolymphatic therapy. In addition, there is no urgent reason for changing the present method as sufficient radiation dose reaches the lymph nodes and the side effects are unimportant.

The radiation dose absorbed by the lungs is kept within reasonable limits with the concentration and volume of radioactive contrast medium as mentioned. The only way to completely prevent radioactive material from entering the lungs is to drain the thoracic duct during the first days following intralymphatic application (1). Such a radical measure would only be justified if the radiation dose to the lungs were shown to damage lung function. Radiation doses below 1000 rad are generally well tolerated. Fibrotic changes and disturbances of lung function studies are to be expected with radiation doses exceeding 1400 rad (6).

If by accident the whole amount of 4 mCi ^{32}P and 1 mCi ^{131}I would be injected intravenously, the lungs would have to take a radiation dose of about 2.500 rad. Such an unfavourable situation, however, should not arise if all precautions are observed, particularly if the flow of the radioactive compound is controlled by fluoroscopy (2).

The radioactive substance intended for lymph node irradiation but lost, due to extravasation, can be more or less calculated, and can be taken into account by calculations of the total absorbed dose. Extravasation can be provoked by increasing the speed of injection. It is not yet possible to estimate the therapeutic effect of that measure.

Acknowledgement

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