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Dosimetry in Isolation Perfusion of the Limbs by Assessment of Perfused Tissue Volume and Grading of Toxic Tissue Reactions

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Abstract—*The optimal single dosage of melphalan in isolation perfusion of the limbs for malignant melanoma was assessed. For this purpose a method to determine the volume of the isolated region in the individual patient and a grading system for the reaction of the normal tissues were introduced. A strictly standardized pharmacosurgical routine was developed that permitted an analysis of the correlation between dosage and the grade of toxic reaction in 90 perfusions. The optimal dosage of a cytostatic drug was considered to be the highest amount tolerated at an acceptable risk. Melphalan at 10 mg/l perfused tissue was determined as the likely optimum. This dose provoked remarkably little variation in toxicity, all reactions falling within a safe range. No exception to the applicability of this dosage was encountered.*

INTRODUCTION

REGIONAL perfusion with cytostatic drugs has now been used clinically for 25 years [1]. Despite the high levels of the cytostatics which are attained in the perfusate, the benefit of the treatment has remained limited and uncertain [2]. Limitations inherent to the surgical approach preclude prolonged treatment with dose-fractionation to a cytostatically desirable extent. The real merits should, however, be assessed by controlled clinical studies based on recognized pharmacosurgical principles that are involved in the treatment [3].

Isolation perfusion for malignant melanoma has mostly been performed with L-phenylalanine mustard (melphalan), circulating for one hour together with some other cytostatic drug or as a single agent. We have studied whether a linear increase of the dose of melphalan with the size of the perfused region might be applicable for standardization of treatment. The highest amount of the drug tolerated by the normal tissues at an acceptable risk was considered to be the optimal dosage. Melphalan was used as a single agent. The evaluation of dose–toxicity relations required the introduction of a method to determine the volume of the perfused region in the individual patient and a grading system for the toxic reactions of the normal tissues.

METHODS

The *determination of the regional tissue volume* [3, 4a] is performed with the aid of cylindrical water reservoirs with diameters of 30 and 15 cm for legs and arms respectively. Connections with piped water and taps facilitate filling and emptying. The transparent walls are calibrated. Safe measurement of a leg requires the possibility of moving the patient up and down on a sturdy platform with support for his/her erect position. The procedure is schematically presented in Fig. 1. The leg is sunk into the reservoir while this is empty. When the patient rests with his perineum on the rim the reservoir is filled completely. Withdrawal of the limb from the reservoir by raising the patient causes

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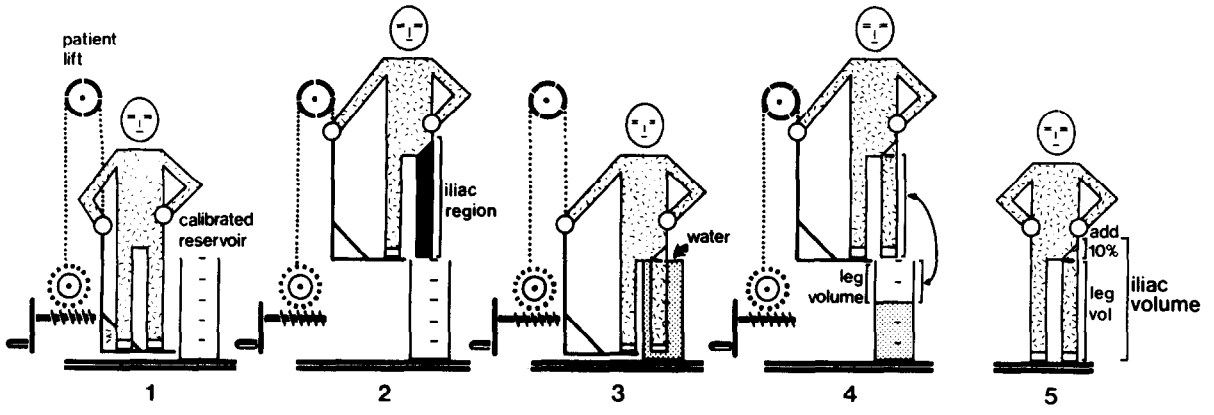

Fig. 1. Procedure to determine the iliac perfusion volume.

a lowering of the water level which is proportional to the immersed part of the leg. A 10% correction is added for that part of the iliac perfusion region which cannot be submersed. All other regions (femoral, popliteal, axillary, branchial) can be determined completely by immersion of the limb to the level of the planned isolation.

Comparisons of regional volume with body weight were made on the assumption that the specific gravity of the tissues concerned is 1.0. Therefore one litre represents one kilogram.

The following *grading system of the toxic reactions of the normal tissues of limbs to melphalan* [3, 4a] was used:

Grade I: No subjective or objective evidence of reaction.

Grade II: Slight erythema and/or edema.

Grade III: Considerable erythema and/or edema with some blistering; slightly disturbed motility permissible.

Grade IV: Extensive epidermolysis and/or obvious damage to the deep tissues, causing definite functional disturbances; threatening or manifest compartmental syndromes.

Grade V: Reaction which may necessitate amputation.

Certain considerations have influenced the individual classification. The peak of a reaction determined its grading. Though this too might be a parameter, the duration of a reaction was not taken into account. Lymphadenectomy performed in combination with the perfusion may interfere with the classification of a toxic reaction; in such cases, erythema was considered more decisive to the grading than edema of the subcutis. Reactions of different grades may be observed within the perfused part of the limb; in such cases, the severest reaction was recorded. If a difference in the severity of the reaction occurred between superficial (skin, subcutis) and deep (muscle) tissues, both grades were taken into account; for instance, grade II/III.

Throughout the investigation grade II and III reactions were considered to be compatible with complete recovery. They were, therefore, accepted as indicators that the optimal dosage had been applied [3, 4a]. In this approach, grade I reactions betray underdosage while reactions surpassing grade III are seen as complications.

The question of whether this grading system may be useful in perfusions of the limbs with other drugs than melphalan requires further attention.

A total of 237 patients suffering from malignant melanoma or sarcomatous diseases of the limbs were treated with regional perfusion of cytostatic drugs in the Antoni van Leeuwenhoek Hospital or the Dr. Daniel den Hoed Clinic between 1975 or 1973 respectively and 1 July 1981. The indications for this treatment, as accepted by the two institutes for five years, are not considered here [4d].

Some years of experimentation and experience have been necessary to achieve a standardized *pharmacosurgical technique* with recording of data that allowed the planned dose–toxicity study. About half of our cases were used for the analysis of one or more aspects of our problem. Primary perfusions dominate this material, though a few cases are included in which the toxic reaction of a preceding perfusion had apparently subsided completely. Perfusion treatment was not attended with mortality. Though perfusion surgery is relatively simple, some particulars of our routine and their motivation have to be considered because of their impact on the dose–toxicity relations.

Periods of oxygen depletion are inevitable during the canulation and the re-establishment of the normal circulation. As these may impair

the tolerance of the normal tissues it is essential to keep them as short as possible. The first anoxic period rarely exceeded three minutes, mainly because the perfusion was started as soon as the canulae were introduced far enough to prevent leakage of blood. With the vessels filled and the venous valves opened up, the advancement of the canulae to the desired position offered no problems. The second anoxic period usually lasted less than ten minutes. This was achieved mainly by washing the vascular tree at an equal or a slightly higher flow rate than applied during the perfusion proper. In this way 150 ml of low molecular weight dextran per litre of perfused tissue could be flushed through the region in about five minutes. Some time could be gained from the use of a longitudinal incision of the vein, as this often allowed side-clamping and restoration of the blood flow prior to closing of the venotomy.

Protection of the normal tissues is aimed at by avoiding hypoxia during the perfusion. As in total-body perfusion, physiological flow rates are employed, checked by gas analysis of the venous blood. For practical purposes flow rates of 30–40 ml/min/l of perfused tissue at temperatures of 37.0–38.0°C are assumed to be physiological or slightly higher.

For the same reason venous congestion is avoided in our perfusion technique. Direct pressure reading from a canula in a peripheral vein is indispensable. Pressures surpassing the preperfusion level by more than 10 cm are considered unacceptable. Free venous outflow may be hampered by a canula which is either too narrow or too wide. Too heavy suction may result in collapse of the vein at the tip of the canula and, consequently, peripheral congestion. At the chosen flow rate, the pressure gradient over the venous canula should compensate the siphon suction pressure of the extracorporeal system. In iliac perfusions of adult's venous canulae of 40 cm length and internal diameters of 4–5 mm are required [3].

The perfused region is warmed by means of a heat exchanger in the extracorporeal circuit and a hot water mattress around the limb. During the whole 60 min of melphalan circulation the regional tissue temperatures are between 37.0 and 38.0°C. This *controlled normothermia* has been considered to be attended with the same tolerance to melphalan as moderate hyperthermia [3].

The effectiveness of the isolation is continuously checked by means of radiolabeled serum albumin prior to and during the perfusion of melphalan.

We try to obtain immediate homogenous distribution of the melphalan in the perfusate in order to promote standardization and to facilitate pharmacokinetic studies. The circulation time is assessed by a pulse of radioisotopes. This determines the speed of the motor-driven injection of melphalan into the arterial line. Melphalan levels in the perfusate are followed with time [4b].

Prophylactic fasciotomy was not performed as grade IV reactions (see below) were considered unlikely because of the minimized risk of muscular damage due to lack of oxygen and venous congestion [3, 5].

RESULTS

The relationship between the volume of the iliac perfusion region and body weight was determined in 93 patients, and between axillary perfusion volume and body weight in 29. The results are presented in Figs 2 and 3. The percentages varied from 11.0 to 21.0 for the iliac region (median 14.7%, mean 15.9%) and from 2.7 to 5.4 for the axillary region (median 4.5%, mean 4.4%). These ratios, representing roughly a variability of ± 1/3 from the mean

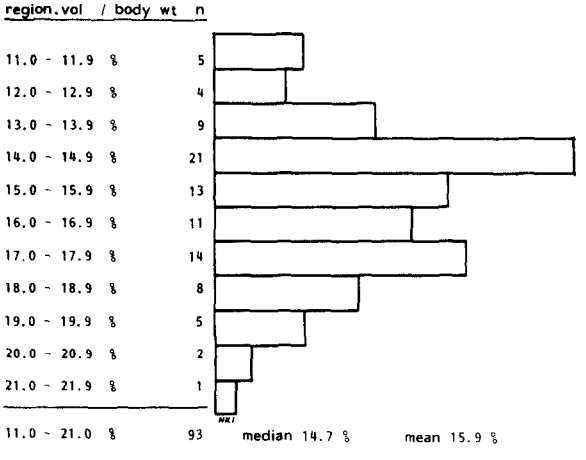

Fig. 2. Distribution of ratios between regional volumes and body weights in 93 iliac perfusions.

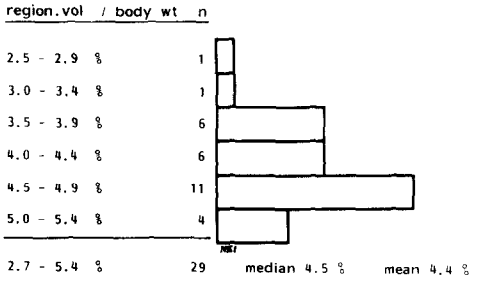

Fig. 3. Distribution of ratios between regional volumes and body weights in 29 axillary perfusions.

values, did not differ significantly between the two sexes.

The administered doses of melphalan, expressed in mg/l tissue volume, are listed in Table 1. Early cases of the series were treated with 0.5–1.5 mg/kg body weight, which resulted in a few instances in a rather low or comparatively high dose, expressed in mg/l perfused tissue. A dose of 10 mg/l was considered to be the optimum at the time our technique had been standardized [4c]. Therefore, this dose, used in 66 cases, predominates in the material. Leakage of the isolation has in no instance been a reason to interrupt a perfusion or to add melphalan in the course of the therapeutic circulation.

The relationship between the administered dose of melphalan and the toxic reaction of the normal tissues could be assessed in 90 patients, 71 of whom underwent an iliac perfusion and 19 an axillary perfusion. The observations are summarized in Table 1. A dose lower than 9 mg/l caused reactions up to grade II. A dose of 13 mg/l or higher invariably caused reactions more severe than grade III. In the group of 78 patients who were treated with 9–11 mg/l, 76 (97%) developed a grade II/III reaction. Of the remaining two patients, one exhibited a grade IV, the other a grade III/IV reaction. In none of the 90 patients was the viability of the limb considered in danger during any phase of the postoperative period.

As the reactions were considered to be toxic–inflammatory, our treatment consisted mainly of rest and avoidance of circulatory stagnation. The majority of patients could be discharged from the hospital two to three weeks after the perfusion. Three of the four patients who exhibited a reaction surpassing grade III benefited, at least subjectively, from prednisolone, 10 mg 3 times daily for 4–7 days [4d]. Fasciotomy to arrest an imminent compartmental syndrome [6, 7] was never indicated.

A comparison between the toxic reactions after iliac and axillary perfusions with 9–11 mg melphalan/l perfused tissue is presented in Table 2. No gross differences are distinguishable with our grading system. In the axillary perfusions the toxic reactions tended to surpass grade II more often than in the iliac perfusions, but reactions in excess of grade III were observed exclusively in two iliac perfusions.

For comparison with the literature [8–12], the dosage in the 78 patients who were treated with 9–11 mg/l have been converted to mg/kg body weight (Table 3). For lower limb perfusions our doses showed a range of 1.07–2.10 mg/kg and for upper limb perfusions, 0.32–0.52 mg/kg. The mean values and standard deviations were 1.58 ± 0.23 and 0.43 ± 0.06 mg/kg respectively. The maximum dose recommended in the literature for iliac perfusions, 1.5 mg/kg body weight, has been exceeded in 40 out of 62 patients who were evaluable for regional toxicity in the lower limb. In axillary perfusions, 14 out of 16 patients received a somewhat lower dose than the lowest one recommended by the literature for upper limb perfusions: 0.5 mg/kg body weight. The grades of regional toxicity

Table 1. Correlation between melphalan doses, expressed in mg/l *perfused tissue, and toxic reactions of the normal tissues graded as discussed in Methods*

Melphalan dose in mg/l*	No. of patients: iliac/axillary perfusions	Reactions of the normal tissues I	I/II	II	II/III	III	III/IV	IV
<7	5/0	3	—	2	—	—	—	—
7–9	4/0	—	1	3	—	—	—	—
9–11	62/16	—	—	57	9	11	1	1
11–13	—	—	—	—	—	—	—	—
13–17	0/2	—	—	—	—	—	—	2
19	0/1	—	—	—	—	—	1	—

*7–9: 7.0–8.9 included, etc.

Table 2. Comparison of toxic reactions in iliac and axillary perfusions, performed with 9–11 mg *melphalan/l tissue*

Perfusion type	No. of patients	Reactions of the normal tissues I	I/II	II	II/III	III	III/IV	IV
Iliac	62	—	—	48	3	9	1	1
Axillary	16	—	—	9	5	2	—	—

Table 3. Comparison of melphalan dosages applied in lower and upper limb perfusions at various centres

Centre	Melphalan dosage in mg/kg body wt		
	Perfusions of lower limb	Perfusions of upper limb	Reference and year
Houston (St. Joseph)	0.9‡	?	[8] (1975)
Houston (Anderson)	1.5	1.0	[9] (1975)
New Orleans (Tulane)	1.0–1.4*	0.6–1.1†	[10] (1979)
New York (NY Univ.)	1.0–1.5	0.75–1.0	[11] (1979)
Groningen (Univ.)	1.0–1.5	0.5–0.7	[12] (1981)
Amsterdam/Rotterdam	1.07–2.10	0.32–0.52	This paper

*Maximally 90 mg.
†Maximally 60 mg.
‡Average.

observed in these two subgroups are presented in Table 4. Here again, no significant difference between the reactions of legs and arms was found.

DISCUSSION

In this study the optimal dosage of a cytostatic drug was considered to be characterized by definite but spontaneously reversible side effects. A distinction was made between a desired reaction of the normal tissue of the perfused limb and a reaction which is either too light or too severe, indicating underdosage and overdosage respectively.

We studied the use of a constant dose per unit tissue volume for the practical reason that the volumes of tissue to be perfused vary markedly and cannot be expected to parallel body weight closely. In our series, the regional volumes varied from 1.7 to 16.5 l; the total doses of melphalan ranged from 17 to 165 mg. The regional volumes in percentages of body weight showed roughly a variability of ± 1/3 from the mean values.

Notwithstanding these variations and the wide deviations from doses recommended in the literature, the observed toxic reactions varied remarkably little. Our pharmacosurgical routine may be expected to be accompanied by little variation in the tolerance of the normal tissues. Therefore, the relatively constant response of the normal tissues suggests the reliability of the dosimetric principles followed in this study. In this connection it may be noted that additional considerations concerning general condition, age, colour of hair and type of complexion [9, 13] have not influenced our dosages. We have no reasons to regret this simplification.

Table 4. Comparison of regional toxicity in iliac perfusions, performed with melphalan dosages exceeding 1.5 mg/kg *body wt, and axillary perfusions, performed with less than* 0.5 mg/kg *body wt, all dosages being chosen on the basis of* 9–11 mg/l *perfused tissue*

Perfusion type	No. of patients	Reactions of the normal tissues				
		II	II/III	III	III/IV	IV
Iliac	40	28	2	8	1	1
Axillary	14	9	3	2	—	—

In perfusion chemotherapy the size of the lower limb appears to be relatively underestimated. This can be inferred from published flow rates as well as applied melphalan dosages. In iliac perfusions roughly 1.5–2 times higher flow rates are used than in axillary perfusions [9–11, 13, 14]. Generally speaking, a 1.7 times higher total melphalan dose is applied in lower limb than in upper limb perfusions (Table 3). These ratios are disproportionate to the ratio of 3.7:1 that we calculated for the mean volume of the iliac region compared to that of the mean axillary volume. In this connection it should be realized that perfusion serves two functions: transportation of the cytostatic agent and replacement of the physiological blood flow in the isolated region [3]. Subnormal flow rates, as often used in lower limb perfusions, may impair the tolerance of the normal tissues and, therefore, may necessitate low melphalan dosages. Recognition of all physiological and pharmacological implications of regional perfusion with cytostatic drugs and strict recording of desired reactions apart from complication rates will be required to compare results from various centres.

Like others, we use the same heart–lung machine for all perfusions. The volume of the perfusate is mainly determined by the priming volume of the apparatus since the amount of blood in legs as well as in arms is relatively small. As our melphalan doses in iliac per-

fusions have been several times higher than those in axillary perfusions, the initial melphalan levels in the first were higher than those in the latter. According to the time course of drug disappearance observed so far, this might lead to some differences in the relative uptake of the drug in legs and arms. This was not reflected, however, in the reactions of the normal tissues, but the number of axillary perfusions is as yet too small to allow definitive conclusions. Our pharmacokinetic studies must reveal whether the overall uptake of melphalan is influenced significantly by its initial level in the perfusate. If so, there will be *two* parameters for the dosimetry: the size of the perfused region as well as that of the extracorporeal circuit.

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REFERENCES

1. CREECH O, KREMENTZ ET, RYAN RF, WINBLAD JN. Chemotherapy of cancer: regional perfusion utilizing an extracorporeal circuit. *Ann Surg* 1958, **148**, 616–632.
2. AU FC, GOLDMAN LI. Isolation perfusion in limb melanoma: a critical assessment and literature review. In: CLARK WH, JR, GOLDMAN LI, MASTIANGELO MJ, eds. *Human Malignant Melanoma.* New York, Grune & Stratton Inc., 1979, 295–308.
3. WIEBERDINK J. Physiological considerations regarding isolation perfusion of the extremities. Monograph delivered on request by the Netherlands Cancer Institute, Amsterdam, the Netherlands.
4. WIEBERDINK J *et al.* Regional perfusion therapy. Section VIII.4 in *Annual Reports of the Netherlands Cancer Institute,* Amsterdam, The Netherlands (a) 1977, (b) 1978, (c) 1979, (d) 1980.
5. RENEMAN RS. *The Anterior and the Lateral Compartment Syndrome of the Leg.* The Hague, Mouton & Co. 1968.
6. SCHRAFFORDT KOOPS H. Prevention of neural and muscular lesions during hyperthermic perfusion. *Surg Gynecol Obstet* 1972, **135**, 401–404.
7. RENEMAN RS, WIEBERDINK J. A new technique for blind (subcutaneous) fasciotomy of the anterior compartment of the leg. *Arch Chir Neerl* 1970, **22**, 39–43.
8. STEHLIN JS, GIOVANELLA BC, DE IPOLYI PD, MUENZ LR, ANDERSON RF. Results of hyperthermic perfusion for melanoma of the extremities. *Surg Gynecol Obstet* 1975, **140**, 339–348.
9. MCBRIDE CM, SUGARBAKER EV, HICKEY RC. Prophylactic isolation perfusion as primary therapy for invasive malignant melanoma of the limbs. *Ann Surg* 1975, **182**, 316–324.
10. KREMENTZ ET, CARTER RD, SUTHERLAND CM, CAMPBELL M. The use of regional chemotherapy in the management of malignant melanoma. *World J Surg* 1979, **3**, 289–304.
11. GOLOMB F, BROMBERG J, DUBIN N. A controlled study of the survival experience of patients with primary melanoma of the distal extremities treated with adjuvant isolated perfusion. *Proceedings of the Second International Conference on the Adjuvant Therapy of Cancer.* New York, Grune & Stratton Inc., 1979, 519–526.
12. MARTIJN H, OLDHOFF J, SCHRAFFORDT KOOPS H. Regional perfusion in the treatment of patients with a locally metastasized melanoma of the limbs. *Eur J Cancer* 1981, **17**, 471–476.
13. SCHRAFFORDT KOOPS H, OLDHOFF J, VAN DER PLOEG E, VERMEY A, EIBERGEN R, BEEKHUIS H. Some aspects of the treatment of primary malignant melanoma of the extremities by isolated regional perfusion. *Cancer* 1977, **39**, 27–33.
14. STEHLIN JS, CLARK RL. Perfusion of the extremities: techniques. *Cancer Chemother Rep* 1960, **10**, 3–4.