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Continuous leakage monitoring with Sn-medronate - ^{99m}Tc - labelled RBC and hand-held gamma-probe during hypertermic isolated limb and lung perfusion

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SUMMARY: **Continuous leakage monitoring with Sn-medronate - ^{99m}Tc - labelled RBC and hand-held gamma-probe during hypertermic isolated limb and lung perfusion**

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The aim of this study was to analyze the value of continuous leakage monitoring with red blood cells (RBC) labelled with ^{99m}Tc-medronate and an external scintillation detector (surgical probe) in patients treated with hyperthermic isolated limb perfusion (ILP) with tumor necrosis factor-alpha (TNF alpha) and melphalan. Systemic hematological and metabolic profiles and tumor response were determined. The mean isotopically measured leakage was 5.8% per hour. The correlation between the monitored systemic activity in the blood by surgical probe and by blood samplings were calculated. A good correlation was observed between the two techniques. Patients with a low leakage rate showed reduced adverse effect. Real time monitoring of the leakage during ILP obtained with this method seems to be in our experience easy, safe and accurate, and serves as a good guide for the effectiveness of isolation during perfusion.

KEY WORDS: ^{99m}Tc-medronate, surgical probe, isolated limb perfusion, tumor necrosis factor-alpha, melphalan, leakage.

Aim

Isolated limb perfusion (ILP) with melphalan and Tumor Necrosis Factor-α (TNFα) is used in the treatment of advanced tumors arising in the extremities or within a single organ such as the liver or lung . The addition of TNF to melphalan may increase response rates, but the potential for major systemic toxicity has limited its use. In the absence of leakage to the systemic circulation, systemic toxicity is minimal. A critical step for ILP is the accurate and real-time monitoring of the fact that TNF toxic effects become relevant when overcoming the 10% limit of the effective therapeutic dose administered during ILP. The most diffuse procedure for systemic leakage monitoring is based on the utilization of human soluble serum albumin (HSA) labelled with ^{131}I and an external scintillation detector. Due to the non commercial availability of HSA-^{131}I, we have adopted a method based on the *in vivo* RBC labelling with with Sn-Medronate– ^{99m}Tc. *In vivo* stability of ^{99m}Tc-RBC labelling was assessed by monitoring precordial activity in a normal subject, after IV injections of the pretinning agent (15 micrograms/kg) and ^{99m}Tc-pertechnetate 20 minutes later. The 60 minutes' time/activity curve demonstrates a good stability of the radiotracer.

Population and leakage measurement method

Twelve subjects with recurrent melanoma or soft tissue sarcoma of the lower limb and 2 subjects with pulmonary metastatic adenocarcinoma were treated with hyperthermic isolated perfusion and Melphalan (10 mg/L). Six patient were treated also with TNF (2 mg). Any leakage into the systemic circulation was continuously monitored. A small calibration dose of Sn-medronate-^{99m}Tc-RBC (3-5 MBq) was administered into the systemic circulation after surgical isolation of the limb or the lung. A 10-times-higher dose of tracer was injected into the perfusion circuit when perfusion was stable. The gamma-rays were measured with a surgical probe (Neoprobe 2000), positioned above the heart of the patient or above the temporal artery in case of isolated lung. The count rate was corrected for

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the ^{99m}Tc half-life. Leakage from the perfused organ to the systemic circulation resulted in an increase of the baseline count level. LF was calculated by the following equation:

$$LF = (CPM\ systemic - CPM\ baseline)/CPM\ baseline \times Dsyst/Dperf \times Vtotal/Vsyst \times 100\%,$$

where CPM systemic is the systemic count rate observed during perfusion, CPM baseline is the systemic count rate at the beginning of the perfusion, Dsyst is the dose injected into the patient's systemic circulation, and Dperf is the dose injected into the perfusion circuit; Vtotal is the total blood volume (perfusion plus systemic circulation) and Vsyst is the blood volume of the systemic circulation. Blood activity in systemic and perfusion circulation was also measured by blood sampling in a gamma-counter and correlated with the activity measured by external probe in 4 patients.

Results

The mean isotopically measured leakage was 5.9%/hour. Systemic leakage was ≤ 5% in 8 perfusions. The leakage curves correlated with the thermic and volumetric curve obtained by the perfusion circuitry. The activity measured externally by probe showed a good correlation with the blood activity. Patients with a low leakage rate showed reduced adverse effects with respect to patients who had previously undergone ILP with melphalan and TNF.

Conclusions

We believe that the proposed procedure, based on Sn-medronate-^{99m}Tc-RBC as radiotracer and a hand held gamma probe as detector, appears to be technically simple and accurate in the real-time monitoring of perfusion leakage in ILP.