EFFECT OF MICROSPHERES IN INTRA-ARTERIAL CHEMOTHERAPY. A STUDY OF ARTERIO-VENOUS SHUNTING AND PASSAGE OF A LABELLED MARKER

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Degradable starch microspheres (DSM) mixed and injected with a cytostatic drug might improve intra-arterial chemotherapy by increasing the local drug concentration.

Several factors are of importance for an optimal effect of the microspheres, e.g. size and vascularity of the tumour, arterial blood flow and arterio-venous shunts. Therefore, the dose of DSM has to be individualized. A method for continuous monitoring of the effect of DSM was developed. A radiolabelled marker was injected intra-arterially mixed with DSM and mitomycin C. Two kinetic parameters — Passing Fraction and Marker Flow Rate — were found to be influenced by the microspheres and thus seemed to be useful for monitoring the DSM-treatment.

Arterio-venous shunting was measured as passage of 99Tc-labelled macroaggregated albumin through the liver to the lungs. Significant increase of shunting after injection of DSM was demonstrated in 15 out of 19 patients.

Almost no effect of the microspheres was seen in patients with marked arterio-venous shunting or minimal reduction of the marker flow rate, but in others the passage of the labelled marker could generally be significantly reduced.

Key words: Degradable starch microspheres, Intra-arterial chemotherapy, Liver tumours, A-V shunting.

INTRODUCTION

Degradable starch microspheres (DSM) have been used to improve intra-arterial (i.a.) chemotherapy, since the concentration and duration of exposure to the co-injected drug can be increased in the target organ without increased systemic side effects.1-10

In a previous study, patients with liver cancer were treated with i.a. DSM and mitomycin C.11 As judged by angiograms the effect of DSM varied considerably. In some patients 540 mg of DSM totally stopped the arterial flow through the liver, but in others 900 mg had no obvious effect on the passage of contrast medium.

If more than the optimal dose of DSM is given, backflow of microspheres along with the co-injected cytostatic drug to the gastro-duodenal area will induce acute pain, vomiting and possibly mucosal lesions. Thus, it is essential that the degree of vascular occlusion can be determined continuously during each treatment session.

A method was therefore developed for continuously registering the effect of DSM by measuring the passage of 99Tc-methylene diphosphonate (99Tc-MDP) through the liver. The passage of this labelled marker varied considerably between patients.11

It can be anticipated that several factors, e.g. the size and vascularity of the tumour, the arterial blood flow and arterio-venous (A-V) shunts are of importance for the effect of DSM.

This study explores the possibility of individualizing the dosing of DSM based on measurements of A-V shunting and the kinetics of the passage of labelled markers through the target organ.

MATERIAL AND METHODS

Patient data

This report includes 21 patients of whom 12 had primary and 9 secondary non-resectable liver tumours (7 colorectal, 1 gallbladder and 1 pancreatic cancer). Median age was 60 years (range 22–79) and the Karnofsky performance index was 60 or more. Three patients had previously been treated with intra-venous chemotherapy not including mitomycin C. One of these had the previous systemic chemotherapeutic treatment.
therapy combined with radiotherapy to the liver (20 Gy; 1.8 Gy per daily fraction). Four had known extrahepatic tumours at the time of the first DSM-treatment (three lung and one abdominal lymph node metastases).

**Patient evaluation**

Pre-treatment investigations included abdominal CT, chest X-ray and blood samples for measurements of creatinine (CREA), bilirubin (BIL), alkaline phosphatase (ALP), aspartate-aminotransferase (ASAT), alanine-aminotransferase (ALAT), lactate-dehydrogenase, alpha amylase, haemoglobin, white blood cells (WBC) and thrombocytes (TRC). After each treatment session the biochemical liver tests were repeated daily for one week and then weekly together with determination of haemoglobin and blood cells. The patients were re-evaluated for tumour response after two sessions.

**Catheter technique**

In 16 patients percutaneous catheters (7 F, Sidewinder™ II or III, Cordis, U.S.A. or 6.6 F. D A, Surgimed, Denmark) were inserted via the femoral artery. Under fluoroscopic guidance the tip of the catheter was placed in the proper hepatic artery distal to the gastro-duodenal artery. The liver perfusion was controlled by serial angiography performed before and just after each treatment session. Five patients had surgically inserted catheters connected to an implantable injection port (Port-A-Cath™, Pharmacia, Sweden). The perfusion area of these catheters was checked by scintigraphy after i.a. injection of ~$^{99}$Tc$^{m}$-MAA according to a technique reported by others. In the absence of adverse reactions and major circulation through A-V shunts (see below), further DSM-injections containing the radiolabelled marker without the cytostatic drug were given. The treatment sessions were stopped whenever angiographic or clinical signs of total blockade (epigastric pain, nausea, vomiting) of the arterial blood flow through the liver appeared. The treatment sessions were repeated every 6 weeks.

**Injection schedule**

According to the dose-schedule planned for the present study, mitomycin C (Mutamycin®, Bristol, U.S.A.) 20 mg/m$^2$ was mixed with 900 mg of degradable starch microspheres (DSM, Spherex®, Pharmacia, Sweden). The average diameter of the microspheres was 45 µm (more than 90% between 20–70, less than 5% larger than 70 and less than 5% smaller than 20 µm). The total dose was divided into three equal injections containing 300 mg of DSM mixed with the cytostatic drug in 10 ml. To this mixture was added 20–40 megabecquerel of a radiolabelled marker without affinity to the microspheres. Each injection, after vigorous mixing, was given manually during 20 sec and the interval between the injections was generally 2–3 min.

In the absence of adverse reactions and major circulation through A-V shunts (see below), further DSM-injections containing the radiolabelled marker without the cytostatic drug were given. The treatment sessions were stopped whenever angiographic or clinical signs of total blockade (epigastric pain, nausea, vomiting) of the arterial blood flow through the liver appeared. The treatment sessions were repeated every 6 weeks.

**Radionuclide measurements**

This method has been described in detail elsewhere. Briefly, $^{99}$Tc$^{m}$-hydroxymethylene diphosphonate (Osteoscan-HDP®, Mallingckrodt Diagnostica, Holland) or $^{99}$Tc$^{m}$-methylethylene diphosphonate (Tc-MDP, Solco Nuclear, Switzerland) were employed as labelled markers (both below abbreviated as $^{99}$Tc$^{m}$-MDP). Their passage through the liver was continuously registered by a 50 x 50 mm Sodium-Iodide detector situated over the left or right clavicular area (Fig. 1). Using straight-bore collimation, radioactivity lodged in the liver would not disturb the measurements. The detector was connected to a single channel analyzer and a counter from which the counts per second (cps)-values were continuously transferred to a computer. Corrections for decay of $^{99}$Tc$^{m}$ and ‘dead-time’ of the detector were made by the computer in order to achieve a linear system response up to a count rate of 65,000 cps.

Reference doses of $^{99}$Tc$^{m}$-MDP, without DSM or cytostatic drug, were given in order to calibrate the system. The increase in cps-level — difference between plateau level obtained after injection and background level — was set to represent 100% passage of the marker. The plateau level was calculated as the mean of the cps-values during the last 60 sec (within 3 min after start of injection) and

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**Fig. 1.** Monitor system for continuous measurement of passage of radiolabelled substances through the liver.