Potential Advantages of Loco-regional Intra-arterial Chemotherapy

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Abstract. Arterial infusion or perfusion are currently used to treat hepatic tumours, head and neck malignancy, melanomas and sarcomas of the limbs. An experimental study with epirubicin and cis-platinum infused into the hepatic artery was performed. Epirubicin was injected via the systemic vein or the hepatic artery in 27 rats. Cis-platinum was injected via a systemic route or the hepatic artery in 29 rats. Drug concentrations were evaluated in liver and tumour tissues. In the rats the tumour tissue drug concentration after hepatic artery infusion was 6- and 4-fold higher than with systemic infusion for epirubicin and cis-platinum, respectively. Arterial administration appeared to be better than systemic in terms of drug concentration within the tumours and systemic toxicity.

Arterial infusion or perfusion are currently used to treat several tumours, such as hepatic primary tumours or metastases, head and neck malignancy, melanomas and sarcomas of the limbs. These procedures are applied with the intention of obtaining a high drug concentration within the tumour tissue and low systemic drug levels, thus, avoiding systemic toxicity.

The rationale arose from studies of the vascular patterns of the tumours (1-3) and pharmacological models showing the therapeutic advantage of intra-arterial as compared to systemic chemotherapy. These models calculate the theoretical advantage of loco-regional chemotherapy by using easily obtained parameters, such as blood flow of the target region, total body clearance of the drug and the target organ or body district drug extraction rate (4-6).

However, these studies did not take into consideration the role of rapidly formed drug metabolites within the tissues, which can be released during administration, and that the high uptake by the target organ does not necessarily imply an increase in drug uptake by tumour cells. Therefore, we way consider the Van de Velde statement: "Important pharmacokinetic data for pharmacological evaluation of various methods of administering chemotherapy could be obtained when efforts are devoted to measure drug (and metabolite) concentration within the tumour" (7).

We present our experimental experience with drug tissue concentration in metastases and normal liver after systemic or hepatic artery administration of drugs with high (epirubicin) and low (cis-platinum) hepatic extraction rate.

Materials and Methods

Sprague-Dawley rats (body weight 160-300 g) bearing liver metastases were used. Liver metastases were obtained by injecting a viable cellular suspension of W-256 carcinoma into the portal system as previously reported (8).

Ten days later, rats underwent relaparotomy under ether anesthesia and those animals bearing liver metastases were infused with epirubicin (study 1) or cis-platinum (study 2). At the end of the drug infusion, the animals were sacrificed by exanguination (cardiac left ventricle puncture) and the drug accumulated in the lumen of the hepatic vessels was cleared out by infusing a saline solution both via the hepatic artery and portal vein for 60 sec. The liver of each rat was removed and the tumours were dissected.

Tumours were pooled to obtain samples weighing at least 0.5 g. Liver tissue samples were also obtained from each group.

Study 1. Epirubicin (2.5 mg in 0.5 ml in 40 sec) was injected via a systemic vein (12 rats) or the hepatic artery (15 rats). Tissue samples were frozen at –70°C and kept on dry-ice until use. Tissue levels of epirubicin and its metabolites were measured using highly sensitive high pressure liquid chromatographic (HPLC) with fluorimetric detection and given in μg/g of dry tissue (9).

Study 2. Cis-platinum was injected via a systemic route (13 rats, 0.3 mg/100 g of body weight in 0.5 ml in 40 sec) or via the hepatic artery (16 rats, 0.15 mg/100 g of body weight in 0.5 ml in 40 sec). In addition, in this experiment, the drug concentration was also evaluated in the renal tissue.

The wet tissues were dried and digested and then the platinum was determined as atomic platinum using a atomic absorption spectroscopy.
spectrum (PerkinElmer 1030, PerkinElmer Inc., Wellesley, USA) (10). Platinum values found in tissues are given in ng/g of dry tissue.

Mean and standard deviation of the values obtained for each group of experiments were calculated and the statistical analysis was performed using the Student's t-test.

Results

In study 1, 9 pools of metastases and 9 of liver tissue from rats infused via a systemic vein, and 24 and 9, respectively from those infused via the hepatic artery were obtained. In study 2, the pools of metastases and of liver tissue were 13 and 8 respectively from the rats infused via a systemic vein, and 16 and 8, respectively from those infused via the hepatic artery. Table I summarises the results of the study.

The tumour tissue drug concentration was significantly higher after hepatic artery infusion than after systemic infusion: more than 6-fold in the epirubicin and more than 4-fold in the platinum study.

The drug concentration in the liver tissue was higher after epirubicin than platinum administration. The platinum values in renal tissue were 65.61±8.11 ng/mg after systemic and 27.16±18.48 ng/mg after hepatic artery administration.

Discussion

In our experiments the tumour drug uptake was higher after hepatic artery administration than after systemic infusion, independently of the drug infused.

The liver/tumour drug concentration ratio is more favourable after arterial than systemic administration for both epirubicin and platinum, but, regarding the tumour drug concentration, is more favourable for the latter (0.23 versus 2.7). This is explained by the fact that anthraciclines are highly extracted by the liver in contrast with the lower liver extraction of platinum.

The platinum concentration within the metastases was higher after hepatic artery administration in spite of the fact that the dosage administered to the rats via hepatic artery was half that administered via systemic vein.

It is well known that the main organ of excretion of platinum is the kidney and that renal toxicity is the limiting factor for dosage. The hepatic artery administration of cis-platinum could be considered less toxic compared with systemic infusion considering the lower renal tissue concentration after the former compared with the latter.

Our experimental data are in agreement with those reported by other authors using 5-fluorouracil (11, 12), fluorodeoxyuridine (13), doxorubicin (14) and Adriamycin (15).

Similarly to our experience with hepatic artery infusion, a higher drug concentration in human was reported; for example using Platinum in head and neck tumours (16).

Accordingly with the experimental data, recent clinical experiences in patients with hepatic metastases treated with locoregional infusion showed promising results (17-19). A recent review of 1,086 patients also showed the beneficial role of adjuvant chemotherapy and immunotherapy administered via hepatic artery infusion after hepatic resection for colorectal metastases (20).

Therefore, hepatic arterial administration of drugs seems to be more advantageous in terms of achieving high tumour drug concentration and minor systemic toxicity than the systemic route. This study suggests to examine the pharmacological advantages of hepatic arterial infusion of more recently developed drugs.

References


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