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A comparison of regional versus systemic drug injection

Adriamycin concentration in peripheral blood and gastric stump (post-Billroth II gastrectomy) in the dog

Fang-Ku P'eng, Chew-Wun Wu, Tai-Jay Chang, and Wing-Yiu Lui

Section of General Surgery, Department of Surgery, Veterans General Hospital and National Yang-Ming Medical College, Taipei, Taiwan 11217, ROC

Summary. Gastric stump cancer has a low resection rate and poor response to systemic chemotherapy. This study attempted to achieve higher drug concentrations in target tissues by way of regional arterial injection instead of systemic venous administration. A total of 12 male mongrel dogs that had undergone post-Billroth II gastrectomies were randomly divided into two groups: in group A, 1.27 mg/kg adriamycin (ADM) was injected through the left gastric artery; in group B, the same dose of ADM was injected into a vein in the left front leg. Blood samples were taken at various time intervals, and the dogs were sacrificed 2 h after drug administration. Tissues were removed from various parts of the gastric stump for measurement of the ADM concentration. The ADM content in the jejunum, heart, liver, spleen, and pancreas was also determined. The results were as follows: (1) The ADM concentration in the gastric stump near its lesser curvature and stomal mucosa was significantly higher in group A than in group B ($P < 0.05$). (2) The ADM concentrations in the adjacent organs (heart, liver, and pancreas) were also significantly higher in group A than in group B ($P < 0.05$). (3) The ADM levels in the venous blood were significantly higher in group B than in group A ($P < 0.05$). These results indicate that a chemotherapeutic drug given through the left gastric artery provides a higher drug concentration in the area where gastric stump cancer frequently occurs and that a lower systemic blood level may cause fewer adverse drug effects. The high concentration of ADM in the heart may not be a good indication, but it may serve as an important signal either to select a less cardiotoxic drug or to monitor heart function cautiously during drug therapy.

Introduction

Subtotal gastric resection has for years been the procedure of choice in most hospitals in Taiwan for the management of medically unresponsive peptic ulcers [13]. The increase in partial gastric resections for gastroduodenal ulcers has been correlated with an increased incidence of primary carcinoma in the gastric stump [4, 7].

Offprint requests to: Fang-Ku P'eng, Section of General Surgery, Department of Surgery, Veterans General Hospital, Shihpai, Taipei, Taiwan 11217, ROC

A previous clinical study has demonstrated that gastric stump cancer has a low resection rate and poor response to systemic chemotherapy, and the prognosis is usually dismal [13]. In this study, an attempt was made to increase the local concentration of the chemotherapeutic agent by way of an i.a. instead of i.v. injection to increase the drug's effectiveness.

Since the majority of gastric stump cancers occur after Billroth II (B II) gastrectomy [9, 14], the gastric stump resulting from this surgical procedure was used as the experimental model. Adriamycin (ADM) was chosen as the chemotherapeutic agent in this study since it is now recognized as the most effective single agent for the treatment of gastric cancer [2, 5].

Materials and methods

Experimental design

A total of 12 healthy, adult male mongrel dogs weighing 10–15 kg were randomly allocated into two groups of six. In group A the chemotherapeutic drug was injected through a regional artery, and in group B the injection was given via a peripheral vein; the bolus injection was completed in 5 s.

The dogs were anesthetized i.m. with a priming dose (50 mg/kg) of pentobarbitol sodium, followed by continuous i.v. infusion (5 mg/kg per hour) of the same anesthetic. They were then placed on mechanical ventilation. A conventional distal subtotal gastrectomy with B II anastomosis [3] was done through an upper midline abdominal incision. Briefly, the distal two-thirds of the stomach was resected, the duodenal stump was closed, and gastrointestinal continuity was restored by anastomosing the proximal part of the jejunum to the gastric remnant. Postoperatively the dogs were fed as usual, without special treatment.

After 1 week, both groups of dogs were anesthetized and their abdomens were reopened. An indwelling polyethylene catheter was placed in the inferior vena cava for blood sampling. In group A, 1.27 mg/kg ADM [6] was injected through the left gastric artery, and in group B, the same dose was injected into a peripheral vein in the left front leg. At various intervals (0, 1, 5, 10, 20, 30, 60, 90, and 120 min), blood samples were drawn via an indwelling catheter and placed in polypropylene tubes containing no anticoagulant. The specimens were centrifuged, and the serum was separated and frozen at −20° C until analysis.

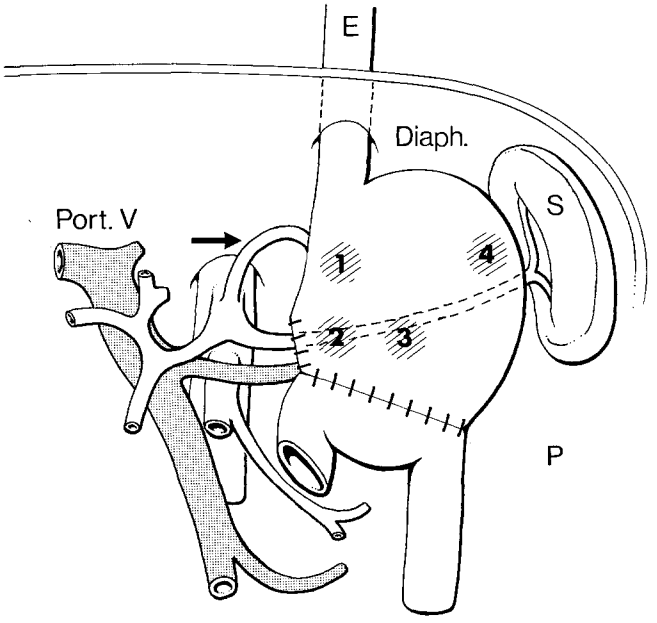

Fig. 1. Representative parts of the gastric stump: site 1, lesser curvature side; site 2, blind end; site 3, anastomotic area; site 4, greater curvature side. *E*, esophagus; *Diaph.*, diaphram; *P*, pancreas; *S*, spleen; *Port. V*, portal vein; *arrow*, left gastric artery

Preliminary studies had shown that optimal ADM levels in tissues were reached 2 h after drug administration; thus, the dogs were sacrificed 2 h after ADM injection. Tissues were removed from the representative parts of the gastric stump (as shown in Fig. 1), jejunum, heart (apex), liver, spleen, and pancreas. The gastric tissues and jejunum were further divided into mucosa and seromuscular layers, which were immediately frozen using liquid nitrogen and stored at −70° C until analysis.

ADM concentration assay

Serum. The serum ADM concentration was determined by the procedure of Benjamin et al. [1]; all samples were analyzed in duplicate. Briefly, the frozen serum was thawed and sonicated to disperse insoluble materials. A total of 4 ml 50% ethanol and 0.15 ml 10 *N* HCl was added to 1 ml serum; the mixture was shaken for 15 s and stored at 4° C for 24 h. The mixture was then centrifuged at 1,300 *g* (Sorvall RT 6000 centrifuge) for 10 min. The supernatant was collected and shaken (Labquake shaker, Labindustries, California) for 20 min after the addition of 6 ml benzene. This mixture was centrifuged at 1,300 *g* for 10 min. The benzene extract was dried under N_2 gas and dissolved in 3 ml 0.01 *M* $NH_4H_2PO_4$ buffer (pH 4.0) containing 35% methanol (v/v). The resulting mixture was then centrifuged at 1,300 *g* for 10 min. The fluorescence of both the supernatant and the total drug was determined in a spectrophotofluorometer (American Instrument Company SPF-125: excitation wavelength, 470 nm; emission wavelength, 550 nm). Massurement of known concentrations (0.5, 0.75, 1.0, 1.5, and 2.5 μg) of ADM standards was also carried out for calculation of and comparison with that of the serum.

Table 1. ADM concentrations in the gastric wall (ng/g tissue ±SEM)

Injection route	Site 1		Site 2		Site 3		Site 4	
	Mucosa*	Sero-muscular layer*	Mucosa*	Sero-muscular layer	Mucosa*	Sero-muscular layer	Mucosa*	Sero-muscular layer
Left gastric artery (group A, $n = 6$)	416.1 ±36.9	254.8 ±33.3	470.5 ±58.4	273.2 ±64.6	524.1 ±79.7	285.5 ±50.1	443.5 ±119.8	150.0 ±53.2
Left brachial vein (group B, $n = 6$)	236.6 ±48.2	150.0 ±44.9	228.6 ±56.6	156.3 ±39.7	226.9 ±51.8	158.2 ±30.7	273.1 ±71.2	117.6 ±33.5

*$P < 0.05$, arterial vs venous group

Table 2. ADM concentrations in adjacent organs (ng/g tissue ±SEM)

Injection route	Heart (apex)*	Liver*	Pancreas*	Spleen	Jejunum	
					Mucosa	Sero-muscular layer
Left gastric artery (group A, $n = 6$)	2019.8 ±347.5	1768.9 ±251.0	338.1 ±80.2	285.8 ±46.5	383.5 ±136.5	160.8 ±56.5
Left brachial vein (group B, $n = 6$)	633.9 ±72.5	833.6 ±141.3	141.9 ±31.5	205.5 ±39.9	241.5 ±31.6	133.8 ±23.5

*$P < 0.05$, arterial vs venous group

Tissue extraction. First, 10 ml acidic methanol was added to 1 g tissue and pulverized with Polyton. The mixture was shaken for 10 min and centrifuged at 500 *g*. Next, 2 ml supernatant was added to a mixture of 2 ml H_2O and 6 ml benzene, and the mixture was then shaken for 10 min. The remaining procedure used for the measurement of ADM in tissues was the same as that described above for determining ADM in serum.

Statistical analysis. Data, expressed as mean ± SEM, were compared in pairs by the Wilcoxon signed rank-sum test [10].

Results

ADM concentration in various sites in the gastric remnant

Table 1 shows that ADM concentrations in sites 1, 2, and 3 were higher in group A than in group B; the differences were statistically significant. The ADM concentration in gastric remnant seromuscular layers of site 1 in group A was significantly higher ($P < 0.05$) than that in group B (Table 1). Apparently, ADM injected through the left gastric artery reached a higher concentration in the area of lesser curvature and around the anastomosis.

ADM concentration in adjacent organs

As indicated in Table 2, ADM concentrations in the heart, liver, and pancreas in group A were significantly higher ($P < 0.05$) than those in group B. The jejunum near the anastomosis and the spleen exhibited no statistically significant differences in ADM concentrations, regardless of the route of administration.

ADM concentration in peripheral blood

As indicated in Fig. 2, the serum ADM concentration peaked 1 min after drug administration in groups A and B. It then fell abruptly to a low level in 20 min. The elimination half-life ($t_{1/2}$) of ADM in the bloodstream was 4 min. The disposition rate of ADM appeared to be a three-phase phenomenon in both groups A and B. Statistically, the serum ADM concentrations were significantly higher in group B than in group A ($P < 0.05$) at all times measured, particularly in the first 20–30 min after injection. This indicates that i.v. injection of ADM results in a very high concentration in the peripheral venous blood, followed by a rapid decreased after dilution by each circulation, whereas i.a. injection results in the retention of high concentrations of ADM in the regional organs.

Discussion

A number of anticancer drugs are now available, but a high priority must be assigned to finding appropriate ways that will maximize their effectiveness. Nearly all anticancer drugs have narrow therapeutic indices, i.e., the most effective dose must be the maximum that the patient can tolerate. The goal of i.a. injection is to increase the therapeutic index by maximizing the drug concentration directly at the site of the lesion while minimizing the side effects.

The data presented here show that a higher drug concentration is obtained when chemotherapeutic agents are given via the regional artery as opposed to a peripheral vein (Table 1). The higher concentrations were noted

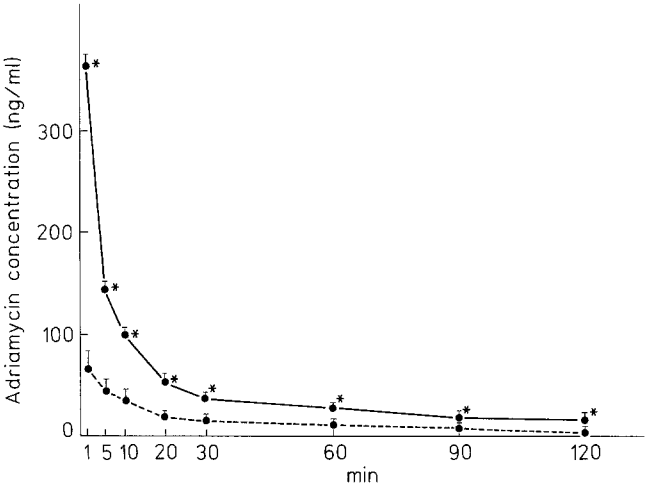

Fig. 2. ADM concentration in venous blood after regional arterial (——— i.a.) vs peripheral venous (– – – – – i.v.) injection. $*P < 0.05$

around the site of lesser cuvature and in the anastomotic area. These areas are frequently involved in cancers occurring after gastrectomy [8, 12, 13]. Clinically, the location of gastric stump cancer can be identified through gastroscopy or by barium sulfate study. Whenever possible, endoscopy and dye instillation via the arterial catheter should be carried out before treatment to assure the proper position of the indwelling catheter for the best drug distribution [11].

In cases of inoperable gastric stump cancer, the tumor invades adjacent organs such as the liver and pancreas [13]. In this study, ADM concentrations in these organs following regional arterial injection were significantly higher than those after peripheral venous injection ($P < 0.05$). This indicates that the injection of ADM via the left gastric artery provides a higher drug concentration in the organs where advanced gastric stump cancer is usually directly involved.

In dogs given the i.a. injection, the ADM distribution in organs other than the stomach was highest in the heart, followed by, in decreasing order, the liver, pancreas, jejunum mucosa, and spleen. The reason for this distribution is not clear. One explanation could be that ADM injected i.a. flows through the stomach, moving to the splenic vein, then through the portal vein to the liver, and, finally, to the heart. The higher drug concentrations in the heart and liver could also have resulted from a 2-h accumulation. On the other hand, in dogs given the i.v. injection, the ADM concentration in the heart was high in the first passage. However, as the ADM concentration in the bloodstream was rapidly diluted, the cumulative ADM concentration in the heart and liver after 2 h was lower than that in dogs given the i.a. injection. This may also explain the higher concentrations of ADM observed in all tissues in dogs given the i.a. injection compared with those in dogs given i.v. ADM. The high ADM concentration in the heart may not be desirable since it is important to select a drug with minimal, if any, cardiotoxicity. However, these findings suggest the need for cautious monitoring of any changes in cardiac function during drug administration.

In this study, the i.a. injection of ADM provided a lower systemic blood concentration than the i.v. injection ($P < 0.05$) (Fig. 2). Thus, it may cause fewer adverse side

effects and allow better toleration of chemotherapy. Chemotherapeutic drug administration through the left gastric artery provides a higher concentration of drug in the area where gastric stump cancer frequently occurs. It is quite reasonable to predict that higher tissue drug concentration will produce a stronger tumoricidal effect. In addition, the i.a. injection of chemotherapeutic agents provides a lower systemic blood concentration than the i.v. injection; hence, it may cause fewer adverse side effects. A high concentration of drug in the heart is not desirable since it is important to select a drug with low cardiotoxicity. We suggest that close observation of possible changes in cardiac function appears warranted during drug administration.

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