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TRANSIENT INTESTINAL ISCHAEMIA INDUCED BY DEGRADABLE STARCH MICROSPHERES

Experiments in the cat

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The basic concept of radiation therapy is tumour eradication without unacceptable injury to normal tissue. This is possible when the tumour is more sensitive to radiation than the normal tissues, i.e. when a therapeutic ratio exceeding one exists. Such a ratio can be raised by increasing tumour sensitivity or by decreasing normal tissue sensitivity.

The search for tumour specific sensitizers has not, up to now, resulted in clinically applicable methods. As oxygen plays an active role in the formation of free cytotoxic radicals mediating the biologic effect of commonly available ionizing radiation for clinical use (photons and electrons), the oxygen tension in the tissues can modify the radiation effect (GRAY et coll. 1953). The sensitivity of hypoxic cells in tumours can theoretically be raised by hyperbaric oxygen treatment at the time of irradiation, and the radiation sensitivity of the normal tissues can be decreased by methods causing hypoxia.

The hyperbaric oxygen treatment principle has been clinically tried (CHURCHILL-DAVIDSON et coll. 1957) but the results have not been convincing, and on account of complications this method is no longer used. Other methods increasing the oxygen content in the tissues by means of peroxide infusion have also been abandoned.

Protection of normal tissues by induction of hypoxia has recently been described. PENN et coll. (1975) demonstrated effective hypoxic protection to radiation of the gut induced by clamping the mesenteric arteries in dogs. STECKEL et coll. (1969 a, b) and JOHNSON et coll. (1968) demonstrated a similar protection of the gut and kidneys using vasoconstricting agents.

ARFORS et coll. (1976), in pigs, induced a transient hypoxia in the small intestine by the injection of degradable starch microsphere (DSM) into the superior mesenteric artery. FORSBERG (1978 a) demonstrated a radiation protective effect on the hind foot and the same author (1978 b) as well as FORSBERG & JUNG (1978) found a similar effect in the small intestine of the rat after hypoxia induced by degradable starch microspheres. FORSBERG et coll. (1979) also demonstrated this protective effect against the development of late fibrosis in the gut wall. These experiments clearly show the possibilities of the hypoxic method for radiation protection already discussed by FORSBERG (1978 a).

In clinical radiation therapy the intestine and kidney are examples of comparatively highly sensitive tissues. Radiation injury to these organs with subsequent intestinal ulcerations, necrosis and stenosis, or renal functional disturbances and hypertension may make it impossible to deliver a sufficient dose to intra-abdominal or retroperitoneal tumours.

The possible clinical use of hypoxia induced by injected degradable starch microspheres for protection of normal tissues unavoidably exposed to ionizing radiation awaits simple, reliable methods to monitor the induced ischaemia. It is not possible to

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use blood flowmeters or oxygen tension meters or directly observe the organ colour at repeated treatment sessions in patients.

The present investigation was intended to assess in the cat (1) the value of a scintigraphic procedure to monitor the degree and duration of intestinal blood flow obstruction induced by the injection of $^{99}Tc^{m}$-labelled degradable starch microspheres into the superior mesenteric artery, (2) the intestinal ischaemia induced by the starch sphere injection, and (3) the intestinal and hepatic degradation of the starch microspheres.

Materials and Methods

Animal preparation. Seven adult male or female cats weighing 3.0 to 5.1 kg were used. The animals were fed on water only during 12 hours before an experiment. The cats were anaesthetized with sodium pentobarbital (40 mg/kg) and kept under light endotracheal anaesthesia after tracheostomy. A cannula (OD 1.02 mm) was inserted into the inferior vena cava through a femoral vein. A second cannula was placed in the left ventricle of the heart through the right carotid artery, and a third was inserted into the abdominal aorta through the left femoral artery and secured with its tip just above the bifurcation. A midline laparotomy was performed, and the main trunk of the superior mesenteric artery was isolated and prepared for measurement of the flow. After isolation and ligation of the distal end of the small ileocaecal branch of the superior mesenteric artery, a plastic cannula (OD 0.63 mm) was inserted and advanced 3 to 5 mm in the proximal direction and fixed in this position with the cannula tip pointing into the main trunk of the superior mesenteric artery, for injection of degradable starch microspheres. Care was taken to secure that the tip of the cannula and the electromagnetic flow probe in the proximal part of the superior mesenteric artery were separated by at least 2 cm. The arterial blood pressure and heart rate were recorded by means of a Statham pressure transducer P23De connected to a Hewlett-Packard 7758 A Recorder. The animals were placed on a heating pad and the rectal temperature maintained at 37 to 38°C.

Degradable starch microspheres (DSM) with diameters of 37.6 ± 5.9 μm suspended in 0.9% saline to a concentration of 13.2×10^{6} spheres/ml (generously supplied by Pharmacia AB, Uppsala, Sweden) were used to produce mesenteric arteriolar occlusion. Before each experiment, about 5×10^{5} spheres were labelled with $^{99}Tc^{m}O_4$ (DJURSÄTER 1979) to a specific activity ranging from 1.5 to 16.3×10^{7} Bq and mixed with unlabelled spheres in a Whirlmixer. When the microspheres were sedimented by centrifugation, less than 10 per cent of $^{99}Tc^{m}$ label remained in the supernatant. The labelled DSM were then resuspended in saline before use. Each animal recieved a dose of 27×10^{6} DSM in a volume of 3.0 ml. The injection time ranged from 75 to 105 seconds.

Carbonized microspheres (CMS; 3 M Company, St Paul, Minnesota, USA), 14.8 ± 1.3 μm in diameter and labelled with ^{46}Sc, ^{51}Cr, ^{85}Sr, or ^{141}Ce, were used to measure blood flow per g of tissue. The microspheres were suspended in 10% dextran with addition of Tween-80 to prevent aggregation. The suspension was sonificated and mixed thoroughly in a Whirlmixer immediately before the injection. The suspensions contained approximately 1.2×10^{6} CMS per ml and were injected into the left ventricle of the heart in a dose of 0.2 ml/kg body weight.

Tissue blood flow was determined by intracardiac injection of CMS and simultaneous withdrawal of a reference blood sample from the aorta at a constant rate as described by HEYMANN et coll. (1977). The net activity of the blood and tissue samples were determined, and the blood flow was calculated from the following formula:

$$QT=QR\times\frac{\text{cpm T}}{\text{cpm R}}$$

where QT=blood flow in tissue sample, QR=blood flow in aortic reference sample, cpm T=counts/min/g tissue, cpm R=counts/min in reference blood sample.

Cardiac output was also determined by the microsphere technique according to the following formula:

$$CO=QR\times\frac{\text{cpm I}}{\text{cpm R}}$$

where QR=blood flow in aortic cannula during withdrawal (1.03 ml/min), cpm I=counts/min of total amount of injected microspheres, and cpm R=counts/min in reference blood sample. Tissue and blood samples were analysed in a multichannel gamma detector (ICN Instruments SC 722, Oakland, California, USA).

Intestinal tissue samples were taken at 9 levels

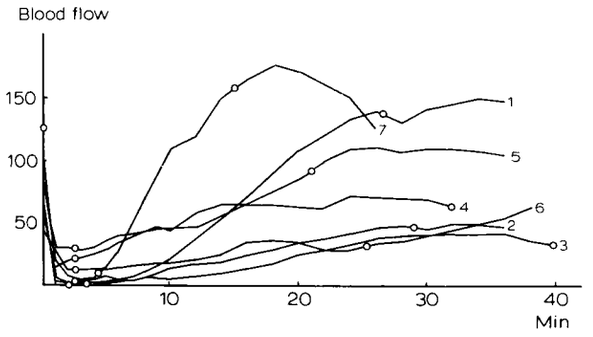


Fig. 1. Electromagnetically measured blood flow (ml/min) in the superior mesenteric artery before and following injection of 27×10^6 $^{99}Tc^m$-labelled DSM into the artery. The symbol O denotes carbonized microsphere tissue flow determinations.

Table 1

Electromagnetically measured blood flow (ml/min) in the superior mesenteric artery following DSM injection

Cat No.	DSM injection		
	Before	3 min after	26 min after
1	105	2	140
2	65	0	47.5
3	110	3.5	38
4	58	22.5	70
5	82	28	112
6	45	12	34
7	87	5	125
Mean + SEM	79±9	10±4	81±17

from 10 to 90 cm from the ligamentum of Treitz. In each sample the 'mucosa' was separated from the 'muscularis' by simple stripping, and the two layers were analysed separately. Microscopic examination showed that the mucosa samples were composed of the following layers: mucosa, muscularis mucosae, and submucosa. An occasional sample contained small strips of smooth musculature. The muscularis samples contained only smooth musculature and the serosal lining.

Serum amylase was determined by standard methods (ZINTERHOFER et coll. 1973) and expressed in arbitrary units (normal range in man: 40–140 units).

$^{99}Tc^m$imaging. Activity emitting from the abdominal area was recorded by a Pho/Gamma camera (Nuclear-Chicago, Illinois, USA) connected to a PDP 8/e Nukab computer (Digital Equipment Corporation, Maynard, Massachusetts, USA). The intestinal and hepatic areas were identified by means of a radioactive marker. By computer integration, the accumulated number of counts over each area was determined at 3-min intervals for at least 27 min following the injection of $^{99}Tc^m$-labelled DSM into the superior mesenteric artery. During preliminary experiments, it was confirmed that the CMS used for tissue flow determinations contributed by less than one per cent to total abdominal activity recorded by the gamma camera. The $^{99}Tc^m$ isotope in blood and tissue samples was permitted to decay for at least 7 days, or 28 half-lives, and the samples were then counted for CMS activity.

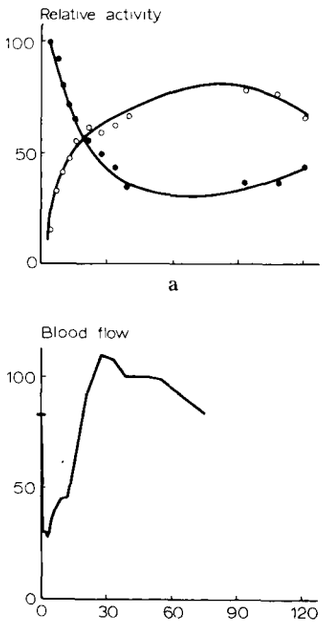
Arterial blood flow in the superior mesenteric artery was recorded by a flow probe with a diameter of 2.6 mm positioned over the artery and connected to a square wave electromagnetic flowmeter (Carolina Medica Electronics, 501, King, North Carolina, USA).

Experimental procedure. After instrumentation, each animal was placed with the center of the abdomen upwards facing the center of the counting head of the gamma camera. The animal was not moved during the subsequent experiment. The first CMS injection was performed. The electromagnetic probe on the superior mesenteric artery recorded blood flow continuously. At time zero, the $^{99}Tc^m$-labelled DSM were injected into the superior mesenteric artery through the cannula placed in its ileocaecal branch. The flow was recorded at one-min intervals. From 2 to 4.5 min following the injection of DSM, a second CMS tissue flow determination was carried out in each animal. After 14.5 to 40 min, when the mesenteric flow was restored to a stable plateau as evaluated from the individual electromagnetic flow recordings over the superior mesenteric artery, a third tissue flow determination was performed. The animal was then killed by intracardial injection of potassium chloride. The liver, pancreas, spleen, and both kidneys were removed and immediately counted for total activity by the gamma camera.

Statistics. Each cat served as its own control. Student's two-tailed t-test for paired data was used to calculate statistical probability. A common test for linear regression was also used for evaluation of the results. A p-value less than 0.05 was considered statistically significant.

Results

Changes in arterial flow. The changes in arterial blood flow in the superior mesenteric artery in the



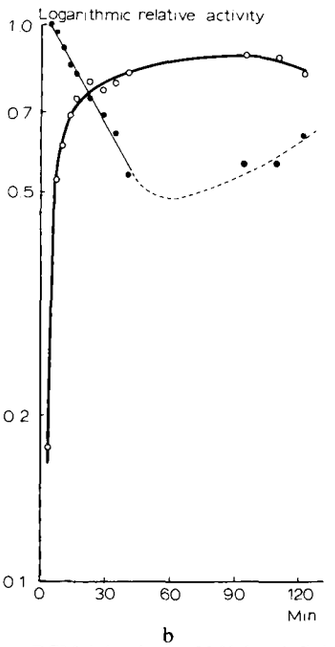


Fig. 2. Observations obtained in cat No. 5. a) Relative activity (in per cent) recorded over intestinal and hepatic areas 3 to 120 min following injection of $^{99}Tc^{m}$-labelled DSM into the superior mesenteric artery. Activity count over the intestinal area 0 to 3 min after DSM injection=100% by definition. b) Semi-logarithmic plot of the data presented in Fig. 4 (100%=1.0). c) Electromagnetically recorded blood flow (ml/min) in the superior mesenteric artery.

seven experimental animals appear in Fig. 1. Each animal was observed until the mesenteric blood flow reached pre-injection control levels or was stabilized. The mesenteric flow decreased to a minimum level 1 to 4 min following DSM injection and gradually recovered thereafter. Control flow value was completely recovered 26 min after the DSM injection in 6 cats, with 3 animals having reactive hyperaemia. In one cat (No. 3, Table 1) complete recovery did not occur, although flow increased markedly from the minimum level. One animal (No. 5) was observed for two hours and had a moderate reactive hyperaemia followed by a gradual decline towards control flow level, which was reached after 75 min (Fig. 2c). Although the variation between the individual cats was considerable, immediate and marked initial flow reduction after the DSM injection followed by flow restoration was consistently reproducible.

Changes in tissue flow. Intestinal CMS tissue flow was repeatedly determined at 9 consecutive levels in samples taken separately from the mucosa and the muscularis (Fig. 3). Immediately before DSM injection, a control CMS tissue flow determination was obtained; 2 to 4.5 min after the DSM administration the minimum flow level was determined. A recovery CMS tissue flow determination was performed when the electromagnetic blood flow had reached either pre-DSM-injection levels or a stable plateau phase. Due to individual variations in restoration of mesenteric arterial flow, the time for the third determination ranged from 14.5 to 40 min after the DSM injection (Fig. 1). The determination of the tissue flow demonstrated a highly significant reduction of the mucosal flow immediately following injection of DSM. In 2 of the cats the reduction in tissue flow in the distal ileum was much less than that observed in the proximal region.

A trend towards slightly reduced mucosal recovery flow in the jejunum and part of the ileum was evident when compared with pre-DSM-injection control values. However, at no intestinal level did the difference reach statistical significance ($p>0.05$). In contrast, tissue flow determinations in the muscularis regularly showed reactive hyperaemia, although the difference between control and recovery flow values only reached statistical significance at levels 10, 60, and 70 cm aboral to the ligamentum of Treitz (Fig. 3).

CMS tissue flow values in the liver, pancreas or spleen were not significantly altered by the DSM injection, and cardiac output remained unchanged (Table 2). However, renal tissue flow was significantly reduced. Thus, although intra-arterial injec-

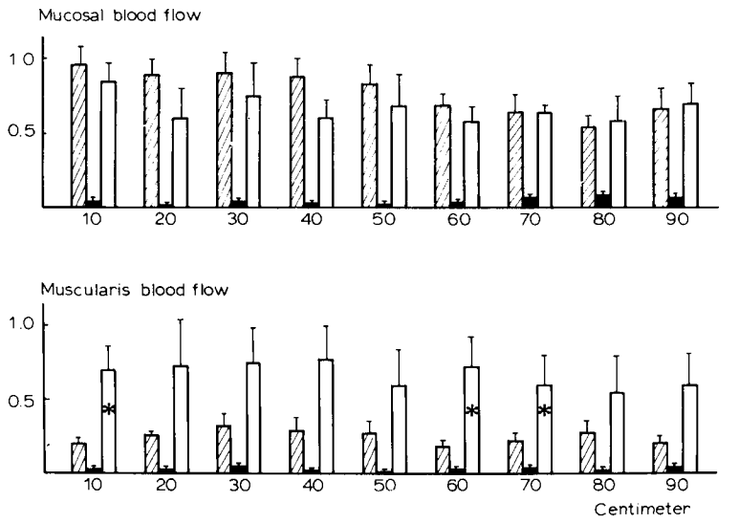


Fig. 3. Tissue flow (carbonized microsphere distribution) in small intestinal mucosa (upper graph) and muscularis (lower graph) before (▨), 2 to 4.5 (■), and 14.5 to 40 min (□) following injection of DSM into the superior mesenteric artery. Mean and SEM of 7 observations obtained at different distances aborally from the ligamentum of Treitz (in cm) are given. *=statistically significant difference ($p<0.05$) between control and recovery values.

tion of DSM profoundly altered intestinal blood flow, the systemic circulation was not compromised except for a transient effect on the renal blood flow.

The CMS tissue flow method and the electromagnetic method measure blood flow at separate levels in the arterial circulation. For each experimental animal, three pairs of simultaneous CMS tissue flow determinations and arterial probe flow readings were obtained, demonstrating a positive correlation between the two methods (Fig. 4).

Degradation and distribution of starch microspheres. Emission from the hepatic and intestinal areas following $^{99}Tc^{m}$-labelled DSM injection was continuously recorded. Since the tracer must pass the mesenteric vascular bed to reach the liver, intestinal activity during the time interval 0 to 3 min following DSM injection was defined as 100 per cent and accordingly the relative activity remaining in the intestinal area and the activity accumulating in the liver was calculated. It is recognized, however, that a minute fraction of $^{99}Tc^{m}$ indicator escaped from the intestinal to the hepatic area during the first 3-min interval, making the defined 100 per cent slightly less than the amount of tracer actually injected into the superior mesenteric artery.

During the first 27 min following $^{99}Tc^{m}$-labelled DSM injection, intestinal relative activity decreased while hepatic activity increased (Fig. 2a) in all animals. The individual semilogarithmic plots of intestinal relative activity transfer demonstrated initial exponential removal of $^{99}Tc^{m}$ and hence of DSM (Figs 2b, 5), while the liver showed rapid initial uptake of $^{99}Tc^{m}$ with a prolonged excretory phase (Fig. 2b). At the end of the experiment, the liver had accumulated approximately 80 per cent of the total activity present in the liver, spleen, pancreas and

Table 2

Tissue flow (ml/min/g) and cardiac output (ml/min) (carbonized microsphere distribution) determined before (control), 2 to 4.5 min and 14.5 to 40 min after injection of $^{99}Tc^{m}$-labelled DSM into the superior mesenteric artery. Mean ± SEM of 7 animals. Asterisk denotes a significant difference ($p<0.05$) from control values

DSM injection	Liver	Kidneys	Spleen	Pancreas	Cardiac output
Before	1.29±0.29	1.99±0.28	2.67±0.52	0.65±0.11	446±61
2 to 4.5 min after	1.13±0.48	1.20±0.21*	2.66±0.48	0.56±0.15	478±55
14.5 to 40 min after	1.26±0.26	2.14±0.18	2.33±0.39	0.99±0.43	408±60

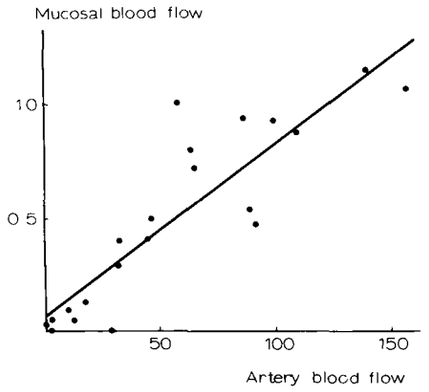


Fig. 4. Relationship between small intestine mucosal blood flow (ml/min/g) CMD and electromagnetically measured blood flow (ml/min) in the superior mesenteric artery. Determinations performed 3 times in each of 7 animals. Mucosal flow values represent means of observations made at 9 levels of the small intestine.

Table 3

Relative $^{99}Tc^{m}$ activity (per cent) in isolated abdominal organs counted by gamma camera after killing the animal. The sum of activity in the liver, pancreas, spleen and both kidneys defined as 100 per cent. Mean ± SEM for 6 animals

	Relative activity
Liver	80±5
Pancreas	7±1
Spleen	2±0
Kidneys	11±4

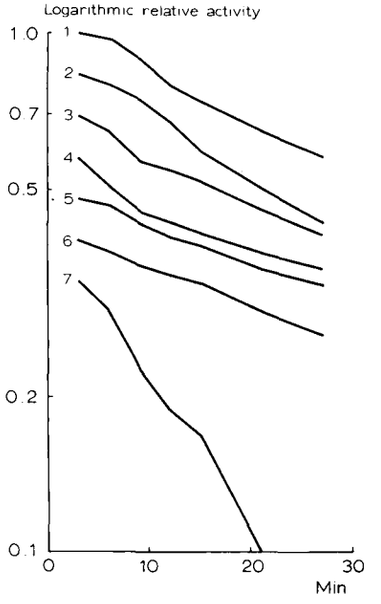


Fig. 5. Semilogarithmic plots. Decline of relative activity over the intestinal area following injection of $^{99}Tc^{m}$-labelled DSM into the superior mesenteric artery. Log activity counted over the intestinal area for 0 to 3 min after DSM injection=1.0. The starting points for each curve on the ordinate scale are separated by a fixed interval for separation of the curves. Values on the ordinate scale are valid for cat No. 1.

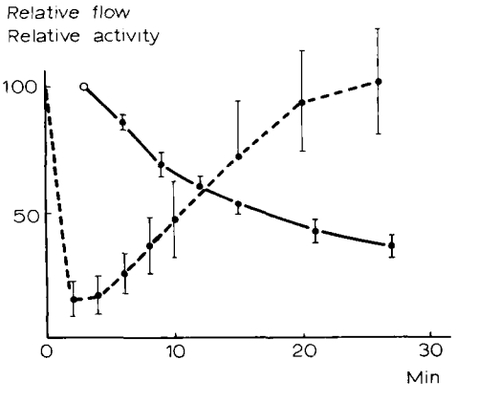
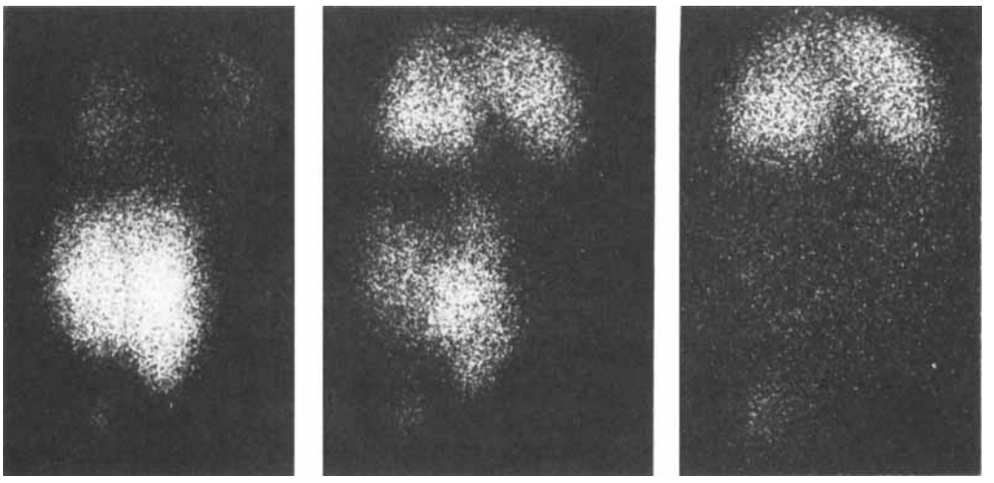


Fig. 6. Relative activity (per cent) recorded over intestinal area (—·—) and relative blood flow (per cent) in the superior mesenteric artery (––·––) following injection of $^{99}Tc^{m}$-labelled DSM into the artery. Activity counted over intestinal area 0 to 3 min following, and arterial flow preceding DSM injection is defined = 100%, respectively. Mean and SEM of 7 animals.

kidneys (Table 3). The gamma camera images taken 3, 18, and 111 min following the injection of $^{99}Tc^{m}$-labelled DSM showed no abdominal hot spot outside the intestinal or hepatic areas (Fig. 7). One cat was observed for 120 min following the DSM injection and showed a late increase in intestinal activity with a concomitant decrease in hepatic activity, indicating recirculation of tracer (Fig. 2 a, b).

As relative activity recorded over the intestinal area decreased, relative arterial flow (per cent of pre-DSM-injection control value) in the superior mesenteric artery increased after a plateau of minimum flow lasting for 4 to 6 min (Fig. 6).

Serum amylase activity (mean 1 450, range 1 030–2 100 arbitrary units) was not influenced by animal preparation or DSM administration. Thus, anaes-



a b c

Fig. 7. Gamma camera images 3, 18 and 111 min following injection of $^{99}Tc^{m}$-labelled DSM into the superior mesenteric artery, demonstrating tracer transfer from the intestinal to the hepatic area (cat No. 5).

thetized cats possess 7 to 15 times higher amylase activity than do resting humans when the amylase activity is determined by the nephelometric method of ZINTERHOFER et coll.

Discussion

Temporary block of mesenteric blood flow in animals or man may be achieved by laparotomy and direct clamping of the superior mesenteric artery, or by catheterization procedures using intra-arterial inflatable balloons. The extensive collateral circulation made possible by the arcading mesenteric arteries will be expected to shorten the length of small intestine rendered ischaemic by these methods. A theoretical advantage of degradable starch microspheres is that they will be carried by the blood stream through the arteries and finally embolize medium-size arterioles (ARFORS et coll., FORSBERG 1978 b), thus minimizing blood flow through collateral vessels.

In the present experiments, selective DSM injection into the superior mesenteric artery immediately and markedly reduced blood flow in the main arterial trunk and in the intestinal mucosa and muscularis. In all but 2 animals blood flow was blocked along the entire small intestine from the duodenum to the caecum. When blood flow in the superior mesenteric artery is arrested, mucosal oxygen is depleted in about 4 min in pigs (ARFORS et coll.), and extensive mucosal injury develops in 1 to 2 hours in animal models (ROBINSON & MIRKOVITCH 1972, RIJKE et coll. 1976), progressing to mesenterial infarction if ischaemia persists. However, mesenteric arterial flow and blood flow in the intestinal mucosa and muscularis were restored at all levels of the small intestine after 26 min in the present experiments. Although one cat (No. 3) showed a 70 per cent reduction in arterial flow, absolute recovery flow was sufficiently high to make intestinal ischaemic damage unlikely.

Intestinal muscle spasm induced by ischaemia (MARSTON 1963, ARFORS et coll.) would increase post-ischaemic intestinal oxygen demand and could explain the reactive hyperaemia consistently found in the muscle layer.

Elimination of DSM from intestinal vessels depends on the separate processes of sphere degradation and wash-out of polysaccharide fragments by the blood stream (ARFORS et coll., FORSBERG 1978 b). The degradation rate is reflected in the exponential elimination of DSM-linked $^{99}Tc^{m}$ from the mesenteric vessels, with an observed mean half-time of 17 min. Individual results (e.g. cat No. 7) indicate that rapid elimination of DSM-linked $^{99}Tc^{m}$ from the intestinal vessels (Fig. 5) may be associated with early recovery of regional flow (Fig. 1, Table 1).

For any degree of DSM-induced arteriolar block, DSM-linked tracer will always be retained in the mesenteric vessels until microsphere degradation permits passage through the capillaries. Blood flow can be measured by isotopic clearance methods if

the isotope is freely diffusible and does not itself influence regional flow (ZIERLER 1965). Neither condition applies to DSM-linked $^{99}Tc^{m}$ clearance from the mesenteric vessels, thus exact calculation of intestinal blood flow from gamma-camera counts is not possible. However, provided a total or near-total arteriolar obstruction is induced, the rate of initial intestinal elimination may permit an estimate of the duration of the resulting intestinal ischaemia (Fig. 6). Early elimination of DSM-linked $^{99}Tc^{m}$ was associated with recovery of intestinal blood flow.

After reaching the liver, $^{99}Tc^{m}$-labelled mono-, di- or poly-saccharides or starch fragments may be retained in hepatic glycogen stores or phagocytosed by Kupffer cells in the liver sinusoids, thus accounting for the observed rapid hepatic accumulation and excretion of activity (Fig. 2b). A continuous $^{99}Tc^{m}$ leakage into and redistribution by the systemic circulation would also be expected. The early, marked deflection of hepatic activity from the straight line in the semilogarithmic plot (Fig. 2b) and the increase in background activity illustrated in Fig. 6, confirm that such isotope leakage did occur. The leakage of $^{99}Tc^{m}$ into the systemic circulation together with possible biliary isotope excretion would also explain the observed simultaneous hepatic decrease and intestinal increase of activity after 120 min.

The present experiments differ from those previously reported concerning temporary regional ischaemia induced by DSM (ARFORS et coll., FORSBERG 1978b, FORSBERG et coll. 1978a, FORSBERG & JUNG 1978, FORSBERG et coll. 1978b, FORSBERG et coll. 1979) in the following respects: a) the detailed tissue flow determinations performed separately in the intestinal mucosa and muscularis along the length of the small intestine, b) the experimental design using the gamma camera to obtain information about intestinal and hepatic degradation of $^{99}Tc^{m}$-labelled DSM, c) the choice of the cat as animal model. The results confirm and extend those of previous reports demonstrating that intra-arterial DSM injection rapidly and consistently induces a temporary circulatory block followed by full recovery of regional blood flow. While the regional use of vasoconstricting drugs to induce a similar degree of ischaemia may adversely affect the systemic circulation (FREEDMAN et coll. 1978), the injections of DSM did not influence cardiac output.

The temporary minor decline in renal blood flow following DSM injection was probably caused by DSM spill-over from the superior mesenteric artery into the aorta and subsequent DSM impaction in the renal arterioles. Such spill-over into a blood vessel other than the injected one may confer hypoxic radiation protection to tumour-bearing tissue and must be avoided.

A plateau of minimum arterial flow lasting for 4 to 6 min was achieved in all animals. Allowing a period of about 4 min to deplete mucosal oxygen (ARFORS et coll.), approximately 2 min are left for delivery of abdominal irradiation while the small intestine still holds hypoxic radiation protection. This is possible with modern linear accelerators delivering 4 Gy/min.

In man, DSM dosage adjustments to the amylase activities met in human blood may be necessary to achieve a temporary flow obstruction of the desired duration. External detection of tracer activity injected with the DSM may offer the clinician a semi-quantitative, non-invasive assessment of mesenteric blood flow, and enable a selection of the appropriate time for radiation therapy.

SUMMARY

Temporary ischaemia was induced in cat small intestine by degradable starch microspheres. Regional arterial and tissue blood flow immediately fell by 85 per cent with subsequent normalization within 26 min after microsphere injection. Degraded $^{99}Tc^{m}$-labelled microspheres were exponentially removed from intestinal vessels and accumulated in the liver. Provided near-total arteriolar obstruction is induced, external isotope detection may permit assessment of the duration of the induced ischaemia, which implies a selection of the appropriate time for radiation therapy.

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REFERENCES

ARFORS K. E., FORSBERG J. O., LARSSON B., LEWIS D. H., ROSENGREN B. and ÖDMAN S.: Temporary intestinal hypoxia induced by degradable microspheres. Nature 262 (1976), 500.

CHURCHILL-DAVIDSON I., SANGER C. and THOMLINSON R. H.: Oxygenation in radiotherapy. II. Clinical application. Brit. J. Radiol. 30 (1957), 406.

DJURSÄTER R.: Personal communication. Pharmacia, Uppsala 1979.

FORSBERG J. O. (a): Transient ischemia for radioprotection. An experimental study with degradable microspheres. Acta Universitatis Upsaliensis, 1978.

— (b): Transient blood flow reduction by intra-arterial injection of degradable starch microspheres. Experiments in rats. Acta chir. scand. 144 (1978), 275.

— and JUNG B.: Modification of abdominal radiation response by hypoxia after intra-aortal injection of starch microspheres. Experiments in the rat. Acta radiol. Oncology 17 (1978), 353.

— JIBORN H. and JUNG B.: The protective effect of hypoxia against irradiation-induced fibrosis in the rat gut. Acta radiol. Oncology 18 (1979), 65.

— JUNG B. and LARSSON B. (a): Modification of radiation response by degradable starch microspheres. Experiments on the rat's foot. Acta radiol. Oncology 17 (1978), 199.

— — — (b): Mucosal protection during irradiation of exteriorized rat ileum. Effect of hypoxia induced by starch microspheres. Acta radiol. Oncology 17 (1978), 485.

FREEDMAN A. R., KERR J. C., SWAN K. G. and HOBSON R. W.: Primate mesenteric blood flow. Effects of vasopressin and its route of delivery. Gastroenterology 74 (1978), 875.

GRAY L. H., CONGER A. D., EBERT M., HORNSEY S. and SCOTT O. C. A.: The concentration of oxygen dissolved in tissues at the time of irradiation as a factor in radiotherapy. Brit. J. Radiol. 26 (1953), 638.

HEYMANN M. A., PAYNE B. D., HOFFMAN J. I. E. and RUDOLPH A. M.: Blood flow measurements with radionucleide-labeled particles. Progr. Cardiovasc. Dis. 20 (1977), 55.

JOHNSON R. E., DOPPMAN J. L., HARBERT J. C., STECKEL R. J. and MACLOWRY J. D.: Prevention of radiation nephritis with renal artery infusion of vasoconstrictors. Radiology 91 (1968), 103.

MARSTON A.: Causes of death in mesenteric arterial occlusion. Local and general effects of devascularization of the bowel. Ann. Surg. 158 (1963), 952.

PENN T. E., PATTERSON W. B. and EDDY H. A.: Protection of normal tissue during X-irradiation by temporary hypoxia. Surg. Forum 26 (1975), 69.

RIJKE R. P. C., HANSON W. R., PLAISIER H. M. and OSBORNE J. W.: The effect of ischemic villus cell damage on crypt cell proliferation in the small intestine. Gastroenterology 71 (1976), 786.

ROBINSON J. W. L. and MIRKOVITCH V.: The recovery of function and microcirculation in small intestinal loops following ischemia. Gut 13 (1972), 784.

STECKEL R. J., TOBIN P. L., STEIN J. J. and BENETT R. L. (a): Intra-arterial epinephrine protection against radiation nephritis. Radiology 92 (1969), 1341.

— — ROSS G., STEIN J. J. and STEVENS G. (b): Radiation protection of vital organs using a selective arterial catheter. Amer. J. Roentgenol. 106 (1969), 841.

ZIERLER K. L.: Equations for measuring blood flow by external monitoring of radioisotopes. Circulat. Res. 16 (1965), 309.

ZINTERHOFER L., WARDLAW S., JATLOW P. and SELIGSON D.: Nephelometric determination of pancreatic enzymes. I. Amylase. Clin. chim. Acta 43 (1973), 5.