Distribution and photodynamic effect of disulphoned aluminium phthalocyanine in the pancreas and adjacent tissues in the Syrian golden hamster

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Summary Necrosis of small volumes of tumour tissue with photodynamic therapy (PDT) can be achieved relatively easily. For this to be clinically relevant, it is essential to know what the same treatment parameters do to adjacent normal tissues into which the tumour has spread. For pancreatic cancers, local spread to vital structures is common. We have studied chemical extraction, microscopic fluorescence kinetics and photodynamic effects of disulphoned aluminium phthalocyanine (AlS²Pc) in normal pancreas and adjacent tissues in hamsters. Chemical extraction exhibited a peak duodenal concentration of AlS²Pc 48 h after sensitisation, with levels much higher than in stomach and pancreas. With microscopic fluorescence photometry highest levels were seen in duodenal submucosa and bile duct walls 48 h after photosensitisation. Pancreatic ducts, duodenal mucosa and gastric mucosa and submucosa exhibited intermediate fluorescence with relatively weak fluorescence in pancreatic acinar tissue and the muscle layer of the stomach. As expected, on the basis of fluorescence intensity and chemical extraction studies, the duodenal and bile duct wall were the most vulnerable tissues to photodynamic therapy. When the dose of 5 μmol kg⁻¹ of sensitiser was used, duodenal perforations, gastric ulcers and transudation of bile from the bile duct occurred. However, the lesions in the stomach and bile duct healed without perforation or obstruction, so only the duodenum was at risk of serious, irreversible damage. Using a lower dose of photosensitiser markedly reduced damage.

It has been shown in many publications that it is relatively easy to destroy small volumes of a wide variety of tumours with PDT (Li et al., 1990; Barr et al., 1991). However, what matters to a patient is whether the entire tumour volume can be destroyed without unacceptable damage to the adjacent normal tissues. This means that it is essential to understand what happens in the region where the tumour is invading normal areas. Surprisingly little work has been done on this aspect (Bown, 1990). Although much of the interest in PDT has centred around the possibility of selective destruction of tumours, this aspect is almost always over emphasised, and getting true and complete selective destruction of cancers is close to impossible (Barr et al., 1990 and 1991). Thus the challenge is to understand what PDT does to normal tissues using treatment parameters that will destroy tumour invading that region. A previous report (Schroder et al., 1988) showed that PDT will produce necrosis in a chemically induced pancreatic cancer in hamsters using dihaematoporphyrin ether (DHE) but at the price of duodenal perforation. The aim of the present study is to look at the effect of PDT on the normal pancreas and adjacent tissues using treatment parameters similar to those known to given pancreatic tumour necrosis to identify which normal tissues are most vulnerable to PDT damage and to find ways to minimise this damage.

Haematoporphyrin derivative (HPD), and purified fractions thereof, are the only photosensitisers currently available for clinical PDT but unfortunately are far from ideal. The properties of more suitable photosensitisers have been identified and sulphonated metallophthalocyanines have been extensively studied in this regard (Bown et al., 1986; Brasseur et al., 1985 and 1987; Tralau et al., 1987; Paquette et al., 1988; Peng et al., 1990), and advantages demonstrated over HPD, including studies involving direct comparison with HPD. The main advantages (Ben-Hur et al., 1987) of phthalocyanines include their strong absorption above 650 nm, where the light penetration of tissue is good, photochemical and thermal stability in solution, relatively well defined chemistry and lower skin photosensitivity to sunlight than HPD (Roberts et al., 1989; Tralau et al., 1989). Both the porphyrins and phthalocyanines may be photodegraded in vivo (Potter et al., 1987; Barr et al., 1990). Most of the PDT studies using aluminium sulphonated phthalocyanine (AlS²Pc) as a photosensitiser, have been carried out using a mixture of compounds with different degrees of sulphonation (range of one to four sulphonated groups, AlSₙPc, where n is 1, 2, 3 or 4; average being 3.2 (Barr et al., 1990; Tralau et al., 1987)). From recent studies (Paquette et al., 1987; Berg et al., 1989; Chan et al., 1990; Chatlani et al., 1991a) disulphonated aluminium phthalocyanine is a more potent photosensitiser than the tetrasulphonated derivative both for in vitro and in vivo studies. For these reasons we have selected the disulphonated fraction, AlS²Pc, for this study.

Chatlani et al. (1991b) have shown that necrosis can be produced by PDT in the same hamster pancreatic cancer model as used by Schroder using AlS²Pc as the photosensitiser. As a prelude for studying the effect of PDT in pancreatic neoplasms, we carried out studies in normal hamsters on the pancreas and its adjacent tissues (duodenum, stomach, bile ducts, portal vein and the main arteries) using treatment parameters similar to those shown by Chatlani (1991b) to produce tumour necrosis. In this paper we studied the distribution of AlS²Pc by both chemical extraction and fluorescence microscopy (Barr et al., 1988; Chan et al., 1989). It has been shown by others that there is good correlation of concentrations measured by fluorescence intensity with those determined by chemical extraction, both with HPD and selectively sulphonated phthalocyanines (Mang et al., 1987; Chatlani et al., 1991a). We also studied the necrosis produced by PDT using high and low sensitising doses of AlS²Pc to establish when damage to normal tissue might be unacceptable, and how this might be avoided.

Materials and methods

Female Syrian golden hamsters weighing 80 to 120 g were used in all experiments. AlS²Pc was separated from an AlSPc mixture, prepared by the olem sulphonation of aluminium phthalocyanine chloride, using reverse phase liquid chroma-
tography (Ambroz et al., 1991). This fraction as analysed by high performance liquid chromatography (HPLC) contains a range of disulphonated components dominated by the most hydrophobic component comprising 60 ± 5% of the integrated HPLC chromatograph. This particular component has been studied by Ambroz et al. for laser spectroscopic investigations, but is difficult to prepare in useful quantities without other components being present. The photosensitiser was administered in isotonic saline by an intracaval injection at laparotomy and the animals were killed 1, 3, 48 and 168 h after the injection. For chemical extractions and fluorescence microscopy studies, the dose of photosensitiser – 5 μmol kg⁻¹ – was chosen on the basis of previous studies (Tralau et al., 1987; Chatlani et al., 1991a). Tissue samples consisting of pancreas, the free edge of lesser omentum, duodenum and middle-distal parts of stomach plus aorta and vena cava were removed at postmortem and immediately frozen using isopentane in a vessel in liquid nitrogen for subsequent fluorescence studies on 10 μm frozen sections. Adjacent tissue samples of pancreas, stomach and duodenum were removed and stored at -4°C prior to chemical extraction. The excretion of AlS₂Pc into bile was studied by cannulating the common bile duct under general anaesthesia and collecting the bile. This was done 1/2 hourly over two 4 h periods (0–4 and 4–8 h) and at 24, 48 and 168 h after sensitisation.

**Extraction of AlS₂Pc**

Phthalalonic acid was extracted from thawed tissues using 0.1 M NaOH (ratio 0.1 g wet tissue 10 ml⁻¹ 0.1 M NaOH) for 4 h in a 50°C water bath. The total tissue phthalalonic acid concentration was measured in the supernatant using spectrofluorometry with calibration against standard curves of known AlS₂Pc concentration (Chan et al., 1988).

**Fluorescence microscopy and photometry**

An inverted microscope (Olympus IMT-2) with epifluorescence and phase-contrast attachments was used, as described previously (Chan et al., 1989). Fluorescence excitation was carried out with an 8 mW helium-neon laser (632.8 nm), with the beam directed through a liquid light guide (via a 10 mm band-pass filter, centred at 633 nm, to remove extraneous light) onto the dichroic mirror (Omega Optical Inc.) for epifluorescence studies. The phthalalonic acid fluorescence was detected between 665 and 700 nm using a combination of band-pass (Omega Optical Inc.) and long-pass (Schott RG665) filters. The imaging detector was a highly sensitive cryogenically cooled CCD (charge-coupled device) camera (Wright Instruments, model 1, resolution 400 x 600 pixels) fitted to the microscope. Image processing and camera operation were carried out by computer. The values for mean fluorescence intensities were calculated by image processing software (Wright Instruments) within rectangular areas of variable size (e.g. 50 x 75 pixels) corresponding to sites of interest. The sections used for fluorescence microscopy were subsequently stained with haematoxylin and eosin for later visual comparison using light microscopy and photography.

The combination of phase contrast microscopy of the frozen sections and light microscopy of haematoxylin-eosin stained adjacent tissue sections enabled different structures of the tissues (serosa, muscle layer, submucosa, mucosa, vessel wall, pancreatic and bile duct wall and acinar pancreas) to be identified in the fluorescence image and the fluorescence intensity of these structures to be measured (Chatlani et al., 1991a).

**Photodynamic therapy**

Light of wavelength 675 nm (peak absorption for AlS₂Pc) from a pulsed (12 kHz) copper-vapour pumped dye laser (Oxford Lasers) was delivered via a 200 μm fibre just touching the surface of the tissue to be irradiated. Control experiments were carried out by looking at the effects of 50 and 100 mW powers at the fibre tip (50J, in either case) on unsensitised hamsters. No thermal effect was detected on stomach or duodenum at 50 mW, although minor changes (oedema and necrosis 0.5 x 1.0 mm) were seen in the pancreas. In contrast 100 mW produced thermal effects, with oedema and necrosis up to 3–4 mm in extent in the pancreas, duodenum and stomach, noted on necropsy specimens, taken at sacrifice 72 h after light exposure. Therefore, 50 mW (X 1000s = 50J energy delivered) was the power chosen for PDT with the fibre tip located on the pancreas (adjacent to stomach or duodenum), the free edge of lesser omentum or the vena cava and aorta, 48 h after sensitisation.

Since with a dose of 5 μmol kg⁻¹ AlS₂Pc, PDT produced duodenal perforations and bile duct necrosis, we also used a smaller dose of sensitiser (1 μmol kg⁻¹ AlS₂Pc) with the same laser power setting and exposure time (50 mW, 1000 s). The animals were killed 72 h after light exposure and changes in treated tissue were studied by macroscopic examination and subsequent light microscopy of haematoxylin and eosin stained sections. Four further animals were treated with 5 μmol kg⁻¹ AlS₂Pc and 50J light, but the duodenum was shielded from the light by gentle mobilisation and insertion of a piece of opaque paper between the duodenum and the fibre tip. These animals were killed 2 weeks after treatment and the treated areas removed for histological examination.

**Results**

**Chemical extractions**

The results are shown in Figures 1 and 2. The concentration of AlS₂Pc was greatest in duodenal wall 48 h after sensitisation (Figure 1). Stomach and pancreas showed relatively low concentrations at all time points studied. The results are expressed in nmol g⁻¹ of tissue (3–5 animals for each point).

The excretion of bile in these animals was fairly constant at approximately 0.1 ml h⁻¹. The concentration of AlS₂Pc in bile with time is shown in Figure 2. The peak value was seen 3 h after an intravenous injection of 5 μmol kg⁻¹ AlS₂Pc and only fell slightly over the next 4 h, but fell to 50% over 24 h. Thereafter, the excretion declined slowly during the following 6 days.

**Fluorescence microscopy and photometry**

Changes in fluorescence intensity levels in pancreas and adjacent tissues with time are shown in Figure 3, 4 and Table I.

**Figure 1** Concentration of photosensitiser (± s.e.d.) measured by chemical extraction vs time from sensitisation with AlS₂Pc 5 μmol kg⁻¹. All layers of the duodenal and gastric wall were included.
A wide range of values was found. Highest fluorescence was present in duodenal submucosa and in bile duct wall 48 h after photosensitisation and had only decreased slightly by 168 h. Artery wall and serosa exhibited high fluorescence intensity at the first timepoint (1 h) but showed decreasing values at all subsequent timepoints. Pancreatic ducts and duodenal mucosa showed intermediate levels with peak values at 3 h. Weaker fluorescence was noted in pancreatic acinar tissue and in the gastric muscle (Figures 6–10).

![Figure 2](image2.png)

**Figure 2** Concentration of AlS$_2$Pc in bile. Logarithmic scale for time (two animals studied at each time point).

![Figure 3](image3.png)

**Figure 3** Fluorescence kinetics of AlS$_2$Pc in different parts of the pancreas and adjacent tissues.

![Figure 4](image4.png)

**Figure 4** Fluorescence kinetics of AlS$_2$Pc in different structures of gastric and duodenal wall.

**Photodynamic effects**

To avoid thermal effects, a laser power of 50 mW was used throughout the study. For studies on the pancreas either the duodenal or gastric lobe of the pancreas (only one point in each animal) was treated. With the higher dose of AlS$_2$Pc, extensive necrosis of the duodenal wall with perforations was noted 3 days after light exposure (Table II). Small areas of necrosis were seen in the pancreas. There were no gastric perforations, but deep necrotic ulcers with full thickness necrosis were seen in the gastric wall, which were sealed by omental fat or the edge of the liver. When the fibre tip was sited on the common bile duct in the free edge of the lesser omentum, necrosis was seen in the common bile duct and gallbladder wall causing bile to diffuse through the wall with yellow staining of adjacent tissues. No perforation of bile ducts or gallbladder wall was discovered. The liver parenchyma close to the position of the fibre tip also showed necrosis. Because of the severe photodynamic effects with the higher dose of sensitiser, 5 μmol kg$^{-1}$, we carried out further experiments reducing the dose to 1 μmol kg$^{-1}$. With the same light dose (50J) there was no photodynamic effect seen in the pancreas, and only mild damage with erosions or small necrotic ulcers in the stomach. However, a concealed duodenal perforation was discovered in one of the two animals treated with the fibre placed on the pancreas next to the duodenum. In the animals treated with duodenal shielding and killed after 2 weeks, there was no evidence of obstruction or perforation of the bile duct, duodenum, stomach or blood vessels.

| Table I | Fluorescence photometry (counts/pixel (mean ± s.d.)) with time from photosensitiser injection |
|---------|------------------------------------------------------------------------------------------------|
| Time (h) | Pancreas | Duodenum | Stomach | Bile duct | Pancreatic duct | Artery wall | Serosa |
| --------|---------|----------|---------|----------|----------------|-------------|--------|
| 1       | 25 ± 2  | 43 ± 8   | 71 ± 9  | 32 ± 9   | 51 ± 10        | 12 ± 5      | 68 ± 9 |
| 3       | 16 ± 2  | 53 ± 4   | 124 ± 15| 35 ± 12  | 48 ± 12        | 11 ± 1      | 106 ± 9|
| 48      | 13 ± 7  | 33 ± 7   | 135 ± 8 | 17 ± 6   | 28 ± 7         | 5 ± 3       | 146 ± 29|
| 168     | 10 ± 3  | 42 ± 14  | 109 ± 12| 18 ± 5   | 44 ± 12        | 5 ± 2       | 120 ± 13|

Fluorescence values are presented as 'arbitrary units' counts/pixel (± s.d.) corrected for autofluorescence. Measurements of the bile duct included all structures of the bile duct wall as well as the main arteries around the pancreas. Measurements of the arteries included all layers of the arterial wall. The fluorescence intensity of the serosa was measured from the serosa located between the pancreas and stomach.
Discussion

To understand the tissue effects produced by PDT, it is essential to know the distribution of the photosensitiser at the microscopic level. Fluorescence microscopy has high sensitivity and has made possible quantitative measurements of photosensitiser distribution. Good correlation between chemical extraction and fluorescence intensity values has been reported previously in normal rat colon sensitised with sulphonated phthalocyanines (Chatlani et al., 1991a). On the microscopic level, the distribution and behaviour of AlSPc depends on the tissues studied and the degree of sulphonation of the dye (Chan et al., 1990; Chatlani et al., 1991a). Reduction in the number of sulphonated groups in AlSPc increases lipophilicity (Berg et al., 1989), which favours the rapid transport of the dye through cell membranes. Furthermore, the less sulphonated fraction (S/Pc ratio 2.0 = AlS2Pc) was shown to be 25 times more efficient in photoinactivation of hamster lung fibroblasts than the more sulphonated fraction (S/Pc ratio 3.6) (Paquette et al., 1988).

In view of its potent qualities as a photosensitiser, AlS2Pc was chosen for our studies. It is clear from these results that
Figure 7  Fluorescence micrograph of common bile duct. High fluorescence in the bile duct wall 48 h after sensitisation compared with adjacent pancreatic tissue as shown in Figure 10. The colour scale and magnification same as in Figure 6.

Figure 8  Fluorescence micrograph of stomach wall 48 h after sensitisation. Note that the maximum fluorescence is half of that in Figures 6, 7, 9 and 10. Muscle layers exhibit low fluorescence (right) and intermediate fluorescence is seen in the submucosa (subm). Same magnification as in Figure 6.

Some of the normal tissues in the vicinity of the pancreas are vulnerable to serious PDT damage, although others are not. With the higher dose of sensitisier, extensive duodenal wall necrosis with perforations and deep gastric ulcers were seen. Our finding is in accordance with that shown in a previous study (Schroder et al., 1988), which also showed vulnerability of hamster duodenal wall to PDT. They used DHE as the sensitisier and exposed the pancreas to laser light 3 h after sensitisation. We also showed damage to the bile duct when the fibre was positioned on the common bile duct in the free edge of lesser omentum. The portal vein and the main arteries adjacent to the pancreas were not damaged. Pancreatic necrosis was detected when the fibre tip was position-
the collagen in the submucosa (Barr et al., 1987) and so one would not expect necrosis in the muscle layer to lead to perforation. Our results suggest that both in the duodenum and the stomach the muscle wall plays some part in maintaining the integrity of the organ after PDT. There may be other reasons for the vulnerability of the duodenum. It was unexpected that the concentration of the photosensitizer should be so much higher in the submucosa of the duodenum than in the submucosa of the adjacent stomach (antrum and body). However, for measurements in duodenal submucosa, as there is no muscularis mucosae, we included the part of the submucosa that extends into the villus which has a dense capillary network supported by collagen tissue (Wheater et al., 1979) where high fluorescence was detected. In contrast, in the stomach where there is muscularis mucosae, the submucosa does not extend up into the villi and this may explain the differences found. The other organ at risk is the bile duct, high fluorescence (Figures 3 and 7) correlating with severe PDT damage although the duct did not perforate in any animal so the damage may be reversible. High levels of sensitizer in the bile duct wall could be due to high concentrations in bile although the relatively low excretion of AIS₂Pc into bile compared with AIS₂Pc values in plasma (unpublished data) did not support this possibility. Also, duodenal submucosa was highly fluorescent in contrast to the epithelium of the duodenal mucosa despite the latter being in closer contact with bile.

We conclude from these studies that the normal pancreas and the major blood vessels are relatively immune from PDT damage, and that the damage to stomach and bile duct is reversible and probably acceptable. The major problem seems to be the duodenum. Great care will be required if this

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**Figure 9** Fluorescence micrograph of pancreas including the main pancreatic duct and large vessels around the pancreas 48 h after sensitisation. Greatest fluorescence is shown in the connective tissue around the vessels. Same magnification as in Figure 6.

**Figure 10** Relatively low fluorescence (dark brown) is seen in pancreatic parenchyma 48 h after sensitisation. Magnification as in Figure 6.
is treated in patients, although an organ as thick as the human duodenum may be much safer than the thin walled hamster duodenum. However, in the human situation, the scale of everything is so much larger that it will be much easier to limit the area exposed to laser light and avoid the duodenum. It is unfortunate that the duodenum is so vulnerable as there are some conditions that might be suitable for PDT in this region, such as small ampullary carcinomas in patients unsuitable for surgery. It is possible that experiments in larger animals may identify treatment conditions that are safe to use in the duodenum, but with the currently available information, it would be wise to exercise caution in this region.

In contrast, these results suggest that it may be possible to treat tumours of the bile ducts, as bile duct damage appears to heal safely without obstruction or perforation. This is supported by a recent case report (McCaughan et al., 1991). Intraductal PDT using DHE as the sensitizer was administered to a woman, who had histologically proven adenocarcinoma of the common bile duct. The patient had had seven PDT treatments over the course of 4 years, with no jaundice and continues in relatively good health.

There is a long way to go before PDT could become relevant in the treatment of pancreatic cancer in man. PDT can only destroy small volumes of tumour tissue, and it would be essential to use it in conjunction with other techniques (e.g. surgery) for removing the main bulk of a tumour. It may be possible to apply PDT to the tumour bed to destroy remaining areas of tumour after resection of a lesion which is macroscopically limited to the pancreas. Our results suggest it would be safe to treat all the surrounding tissues, with the exception of the duodenum. The other major challenge for the clinical use of PDT is to know which areas to treat. PDT is a local treatment, and although the sensitizer is given systemically, tissue effects will only be produced where light is applied. It will be a diagnostic challenge to find out how far the tumour has spread. However, for normal tissues that are not sensitive to PDT damage or which recover from PDT satisfactorily, it should be safe to deliver light to them. PDT will be of most value when relatively large surfaces of normal tissue can be treated to pick up all the small areas of tumour that are not easily detectable.

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Table II  Photodynamic effects 3 days after treatment

| Sensitiser dose | Site of laser fibre | Result |
|-----------------|---------------------|--------|
| 5 µmol kg⁻¹     | Pancreas adjacent to stomach (n = 2) | Full thickness necrosis, deep ulcers, no perforation (n = 2). Pancreatic necrosis. |
| 5 µmol kg⁻¹     | Pancreas adjacent to duodenum (n = 2) | Duodenal perforations (n = 2) with diffuse peritonitis, I dead at 48 h. Pancreatic necrosis. |
| 5 µmol kg⁻¹     | Free edge of lesser omentum (n = 2) | Transudation of bile. No macroscopic perforation of bile ducts (n = 2), but full thickness damage. No damage to portal vein or hepatic artery. |
| 1 µmol kg⁻¹     | Pancreas adjacent to stomach (n = 2) | Partial thickness necrosis with deep ulcer (n = 1) and with superficial ulcer (n = 1). No pancreatic damage (n = 2). |
| 1 µmol kg⁻¹     | Pancreas adjacent to duodenum (n = 2) | Full thickness necrosis with sealed perforation (n = 1), partial thickness necrosis with ulcers (n = 1). No pancreatic damage (n = 2). |
| 1 µmol kg⁻¹     | Free edge of lesser omentum (n = 2) | No transudation of bile, minor necrotic areas in bile duct wall (n = 2). No damage to portal vein or hepatic artery. (n = 2). |

PDT effects in animals killed at 72 h after exposure to 50J. All animals were treated 48 h after intravenous sensitisation with AlS₂Pc.
Chatlanil, Chan, Chan, Chatlanil, McCAughan, Chan, LI, J.H., GUO, Z.H., JIN, M.L.

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