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Photodynamic Therapy for Polyps in Familial Adenomatous Polyposis—A Pilot Study

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Photodynamic therapy (PDT) produces localised necrosis with light after prior administration of a photosensitising drug. As PDT lesions in the gastrointestinal tract heal so well, the technique is suitable for repeated endoscopic use. In this study, PDT was used to treat large polyps (four duodenal and two colorectal) unsuitable for surgery in 6 patients with familial adenomatous polyposis (FAP). Patients were sensitised with 60 mg/kg 5-aminolaevulinic acid (ALA) orally or intravenous (i.v.) 2.0 mg/kg Photofrin. Laser treatment was performed 6 h after ALA or 48 h after Photofrin using a gold vapour laser. Necrosis was only superficial (up to 1.8 mm) using ALA but much deeper using Photofrin. The one malignant polyp (8 mm diameter in the colon) showed a complete response using Photofrin. All healed safely with no complications. Photofrin worked better, but caused cutaneous photosensitivity lasting up to 3 months. ALA cleared within 2 days, but its use is limited by the superficial effect. Better results with ALA may be obtained using higher drug doses or modified light dosimetry. Fluorescence microscopy showed no evidence of selectivity of photosensitisation between neoplastic and normal tissue. PDT is a promising treatment for inoperable polyps in patients with FAP, but further work is required to optimise the treatment conditions.

Key words: familial adenomatous polyposis, photodynamic therapy, endoscopic therapy
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INTRODUCTION

FOR MOST patients with familial adenomatous polyposis (FAP), the main clinical problem is the colonic polyposis, which is normally managed surgically by colectomy. However, many of these patients also develop benign and malignant polyps in the upper gastrointestinal tract, particularly the duodenum, and these are proving difficult to manage. There is increasing evidence that small polyps in the upper gastrointestinal tract, or in the rectal stump after a colectomy and ileorectal anastomosis, respond to anti-inflammatory drugs such as sulindac, aspirin and even indomethacin, but unfortunately the larger polyps do not [1–3]. If necessary, the rectal stump can be removed by further surgery, whereas surgical management of duodenal polyps in these patients has proved most unsatisfactory. Duodenal polyps always recur, and a recent report showed that the median time from surgery to recurrence was only just over a year [4]. Thus, there is a need for a new way to treat these lesions that has no cumulative effects so that it can be applied repeatedly, if necessary, without causing duodenal stenosis or perforation, if lesions recur. If such a technique could be found to treat the larger polyps then, in conjunction with anti-inflammatory drugs, it might be possible to keep the whole disease process in the duodenum under long term control. It is feasible to debulk larger polyps in the duodenum or rectal stump with the NdYAG laser [5], but it is unsafe to use this laser to treat the base of such lesions as there would be a risk of muscle scarring and perforation. Photodynamic therapy (PDT) might be able to solve this problem as it has a greater effect on the superficial layers.

PDT is a non-thermal technique for inducing localised necrosis with light after prior administration of a photosensitising drug. For the treatment of lesions in the gastrointestinal tract, the photosensitiser is given systemically (intravenously or by mouth) and the light delivered to the target area endoscopically. PDT has attracted considerable interest as many sensitisers are retained with a small degree of selectivity in neoplastic tissues compared with the normal tissue in which the tumour arose. However, this aspect is often overemphasised. It is extremely difficult to turn selective uptake of the photosensitiser into selective necrosis. However, the main attraction of PDT is the nature of the healing process as there is much less scarring than after a thermal injury such as that produced by the NdYAG laser alone or by diathermy. In addition, collagen is unaffected after PDT, which means that the mechanical strength of hollow organs is maintained, even in the presence of full thickness necrosis [6].

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A range of photosensitising drugs are currently being assessed, but the ones used in the present study were Photofrin (dihaematoporphyrin ether, DHE) and 5-aminolaevulinic acid (ALA). Haematoporphyrin derivative (Hpd) is a mixture of porphyrins and its partly purified derivative, Photofrin (DHE), contains the active components [7]. This has been extensively studied experimentally [8, 9] and clinically [10, 11], and shown to be effective in treating small tumours of the gastrointestinal tract, both benign and malignant [12, 13]. However, there is the serious side effect that patients may be left sensitive to bright lights for several weeks after treatment, as has been seen in all these series.

ALA is a naturally occurring intermediary in the haem synthetic pathway. This compound has been exploited recently as a new photosensitiser pro-drug which is metabolised in tissue to the active compound, protoporphyrin IX (PPIX). PPIX accumulates within cells as its final conversion to haem, catalysed by ferrochelatase, is the rate-limiting step in this synthetic chain. Photosensitisation obtained in this way has been successfully employed for PDT *in vitro* [14], in animal tumour models [15, 16], in humans after topical administration in the treatment of cutaneous basal cell carcinomas [17], and after systemic administration for the treatment of tumours of the mouth and gastrointestinal tract [18, 19]. There are several advantages of using ALA. Skin photosensitivity is limited to 1–2 days, it can be given by mouth, and PPIX accumulates more in the mucosa of the gastrointestinal tract than in the submucosa and muscle layers [18–21]. The ratio between PPIX levels in large bowel mucosa and the underlying muscle can be as high as 10:1, and it appears to offer slightly better selectivity between malignant and normal tissue [15, 19]. This knowledge has prompted us to study the tissue distribution of PPIX after oral administration of ALA in patients with FAP, and whether ALA given orally is effective in inducing PDT necrosis in these patients upon treatment with red light at 630 nm, which corresponds to the longest wavelength absorption band of PPIX. This paper reports preliminary results using these two photosensitisers for treating polyps unsuitable for surgery in patients with FAP.

PATIENTS AND METHODS

6 patients with FAP with duodenal or rectal tumours were included in this study. All patients were considered unsuitable for surgery at the time of referral. Details are given in Table 1. All patients were initially assessed with endoscopy and biopsy of the relevant area, and were then given ALA for fluorescence microscopy studies [19]. For technical reasons, it was not possible to undertake fluorescence microscopy studies using Photofrin.

All 6 patients were initially given ALA by mouth dissolved in 5–10 ml of orange juice at total doses of 30–60 mg/kg for fluorescence microscopy studies on biopsy specimens. This dose was divided, being given in three or six fractions at hourly intervals. The time intervals were based on a Finnish study showing the plasma half life of ALA to be 50 min with a peak plasma concentration 1 h after oral administration [22, 23]. Biopsies were taken 6 h after the first fraction to assess tumour and normal tissue levels of PPIX. The doses and times were based on our previous experience showing there was less uptake in colon than in the duodenum for normal or neoplastic tissue [19]. The specimens were immediately frozen in a bath of isopentane (BDH Ltd, U.K.), precooled in liquid nitrogen and then stored in liquid nitrogen for subsequent quantitative fluorescence microscopy on 10 μm cryosections [15].

Subsequently, PDT was performed on all 6 patients. 4 were sensitised with ALA and treated 6 h after the initial fraction of ALA (3 with duodenal adenomas and one with adenomas in his rectal stump). 3 were sensitised with Photofrin (2 mg/kg i.v.) and treated 2 days later (two duodenal adenomas with severe dysplasia, one of whom had previously been treated using ALA, and one with a small colon carcinoma). All patients were treated using a gold vapour laser emitting red light at 628 nm as this is the most suitable wavelength for both PPIX and Photofrin. The light was delivered by a single 0.2 mm bare-tipped fibre from the laser, introduced through the biopsy channel of the endoscope and held with the tip pushed 1–2 mm into the surface of the target lesion. The energy delivered to each site was 50 or 100 J (50 or 100 mW for 1000 s) and 2–4 sites were treated in each patient. Follow-up endoscopies with biopsies of the treated areas were undertaken approximately 3 days and 1 month after PDT. Patients given ALA were kept in a darkened room for one night with no further restrictions from the next morning. Patients given Photofrin were advised to avoid bright lights, particularly sunlight, for at least a month, but were advised that reasonable levels of interior lighting would be acceptable.

RESULTS

Fluorescence studies

The fluorescence studies were only able to give measurements of the relative levels of PPIX between the normal and neoplastic tissues in each patient and between patients. There was considerable variation in the absolute values between patients (by a factor of 5), but the striking finding was that the ratio of PPIX concentration between the adenomas and adjacent normal mucosa in the same patient never rose higher than 1.2. The fluorescence results from patients 2 and 4 have been reported in a previous publication [19]. In the patient with the colon cancer (case 1), the PPIX levels were so low that they could barely

Table 1. *Familial adenomatous polyposis (FAP) patients treated with photodynamic therapy (PDT)*

No.	Age/Sex	Previous colectomy	Lesion treated	Previous Nd YAG laser treatment
1.	45/F	No*	Colon cancer	No
2.	39/F	Yes	Duodenal adenoma	Yes
3.	40/F	Yes	Duodenal adenoma	No
4.	45/M	Yes	Duodenal adenoma	No
5.	34/F	Yes	Duodenal adenoma	No
6.	27/M	Yes	Rectal polyps	No

* Left hemicolectomy only because of multiple desmoids.

be detected above the background levels in the fluorescent microscope system.

Photodynamic therapy

4 patients underwent PDT after ALA sensitisation (3 with duodenal adenomas and 1 with a small rectal adenoma) and 3 after Photofrin. Case 1 was treated using Photofrin as she had such low tissue levels of PPIX after ALA. Most of her small intestine had been removed at the time of surgery for multiple desmoids, which presumably impaired absorption of ALA. She had relatively few colonic polyps and only part of her colon had been removed. Further abdominal surgery would have been extremely difficult and risky, justifying the use of PDT for her small colon cancer, which had been detected at a routine screening procedure. The patient who was treated with both sensitisers (case 2) had a duodenal adenoma with severe dysplasia which responded poorly to PDT with ALA. The size of this polyp was such that it was initially debulked with the NdYAG laser before PDT was applied. Case 3 had a similar lesion and, in view of the poor response with ALA in case 2, it was decided to treat her initially using Photofrin. Cases 4, 5 and 6 were treated only with ALA.

In cases 2–6, 3 days after PDT, treated areas were found to be covered with a whitish necrotic material, most marked when Photofrin had been used. After a month, the surface of the adenomas had healed. In cases 2 and 3 treated using Photofrin, there had been a definite reduction in volume of the lesions, although none had been eradicated. Figure 1 shows the ampullary region in case 3 before treatment and 1 and 5 months after treatment. In those treated with ALA, cases 4–6, there was no major change in the lesion size. Case 1 had a flat carcinoma 8 mm in diameter and the follow-up endoscopies were undertaken at different times. At 1 week, there was superficial ulceration involving 50% of the circumference of the colon, including the site of the tumour and surrounding normal mucosa. By 3 weeks, approximately 70% of this had healed and by 6 weeks, it was not possible to identify the exact site of treatment as the mucosa looked macroscopically normal.

For the patients treated using ALA, the changes seen on biopsies taken at 3 days were very superficial. It was difficult to assess the depth of necrosis accurately because of probable sloughing of necrotic tissue at the surface, but it was estimated to be between 0.5 and 1.8 mm (Figure 2). At 1 month, the microscopic appearances were the same as those seen before PDT. The 3 day biopsies in the Photofrin adenoma patients showed deeper necrosis. The biopsies taken at 1 month showed less severe dysplasia than those taken prior to treatment. In case 1, the carcinoma was confirmed on biopsy at presentation, but follow-up biopsies at 6 weeks only showed microadenomas. 18 months after treatment, there was no endoscopic evidence of recurrence. These results are summarised in Table 2.

Side effects

The main concern in patients treated with PDT is skin photosensitivity to sunlight and other bright lights. All patients were given ALA and 5 remained in subdued light for 24 h and had no problems. One who was treated as a day case went home before it was dark, and despite trying to shield herself from the light, did get some reddening of her face, although this resolved without sequelae within a day or so. All 3 patients sensitised with Photofrin had some skin photosensitivity lasting 6–14 weeks. In 2, this was characterised by erythema and swelling of unprotected areas (face and hands), despite their efforts to avoid direct sunlight.

There were no other problems with Photofrin, but after ALA, 2 patients had mild nausea (without vomiting) in the first 12 h, and 3 had transient elevations of serum aspartate aminotransferases (AST), with values less than twice the upper limit of normal. One patient also had a temporary slight elevation of plasma bilirubin level (less than double the normal).

DISCUSSION

This preliminary study has shown that it is possible to produce necrosis in polyps of patients with FAP simply and safely using PDT. The only lesion completely destroyed was the small colon cancer. As the area of necrosis seen in this case was considerably larger than the lesion itself, it is clear that there was no selectivity between the tumour area and normal colonic mucosa, but as the healing was so good, it was not important that there was some damage to normal tissue. Nevertheless, even if the mucosa heals so well that the area treated cannot subsequently be identified, there may be scarring in the underlying muscle. For a small, localised area, this is unlikely to be significant, but if this effect was circumferential, it could lead to stenosis, as has been seen in some patients treated for dysplasia in Barrett's oesophagus using PDT with Photofrin [13]. The other 2 patients in this series treated using Photofrin had multiple and fairly large polypoidal duodenal adenomas (up to 1.6 and 2 cm diameter). In both cases, only the largest lesion was treated (that seen at the ampulla) and no attempt was made to illuminate the entire lesion. This was done at least partly to minimise the risk of biliary obstruction from oedema in the treated area. This did not occur in either patient, although if it was a problem, it could be managed by insertion of an endoprosthesis, which would probably be temporary.

Experimental studies in hamsters have shown that there is a risk of duodenal perforation using PDT with Photofrin [24], but this is probably because the hamster duodenum is extremely thin. Clinical reports of PDT for ampullary carcinomas using Photofrin have not come across this problem [25] and neither did we.

Experimental studies with ALA show preferential photosensitisation in the mucosa of hollow organs compared with the underlying muscle, so that it may be possible to destroy epithelial tumours with less risk to deeper layers, even if there is some necrosis of normal mucosa [21, 26]. Unfortunately, the clinical results with ALA showed that the effect is very superficial, with necrosis no more than 1.8 mm deep, so that we did not achieve significant reduction in the bulk of the polyps treated. Nevertheless, experimental studies on a transplanted tumour in the hamster pancreas have shown that it is possible to produce tumour necrosis 8 mm deep using a higher dose of ALA [27]. Our own preliminary experimental studies [28] suggest that the maximum dose of ALA that patients can tolerate by mouth (60 mg/kg) is only just enough to reach the threshold for a PDT effect, so further developments in this area will have to await an intravenous preparation of ALA suitable for clinical use so that a higher dose can be administered. It has previously been shown that for comparable tissue levels, the dose required by mouth is double that required if given intravenously [21]. In addition, as skin photosensitivity only lasts a day or so after ALA, if reasonable necrosis can be achieved, treatment could be repeated at quite short intervals, which is not feasible using Photofrin [13, 29].

Our pharmacokinetic results on the adenomas show essentially no difference in the tissue levels of PPIX between adenomas and adjacent normal mucosa. Light was only delivered to the

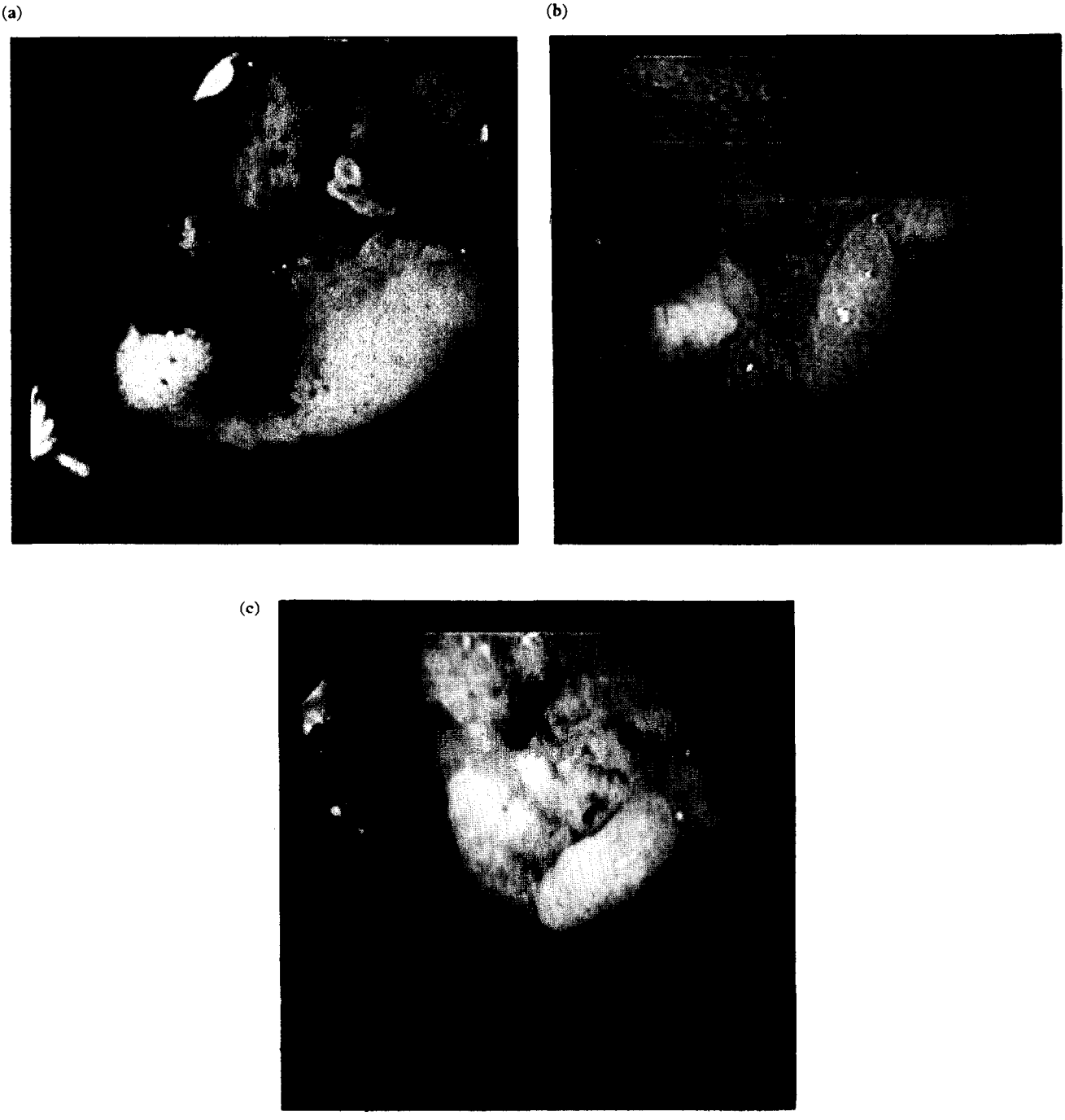

Figure 1. Endoscopic views of ampullary polyp in patient 3: (a) prior to treatment; (b) 1 month after PDT; (c) 5 months after PDT. The initial bulk of friable adenoma around the ampulla is seen to be considerably reduced in the follow-up photographs.

adenomas and not to adjacent normal mucosa, so the PDT effects were limited to the adenomas, but if the intention was to treat entire lesions, it is clear that there would be just as much damage in the normal mucosa exposed to the same light dose. The only selectivity of effect we could anticipate would be between normal mucosa and the underlying muscle. In a recent report from this centre, a small degree of selectivity was seen in PPIX levels in colorectal cancers compared to the adjacent normal mucosa [19] but in the colon cancer patient in this series, fluorescence levels were so low that no comment could be made about relative tissue levels of PPIX. However, even if selectivity of tissue levels of PPIX could be demonstrated, it is unlikely that this could be turned into selective necrosis of the cancer.

Another aspect of interest is the histological changes after treatment. One aim of treatment is to remove the bulk of large polyps, particularly in the duodenum, but it would also be preferable if the mucosa at the treated site after healing was less dysplastic. In the patients treated with ALA, the microscopic appearances at 1 month were the same as those before treatment, probably because the treatment had done no more than remove a superficial layer of the adenoma. However, in the two duodenal lesions treated with Photofrin, the biopsies at 1 month showed less severe dysplasia. This may have been due to sampling differences, but it raises the possibility that in treated areas, healing may be with less abnormal mucosa. This has been seen in the mouth where areas of severe dysplasia treated with PDT

Table 2. Results of photodynamic therapy (PDT)

No.	Sensitiser/dose per mg/kg/route	Endoscopy findings Initial	3 days after PDT	1 month after PDT	Histology Initial	1 month after PDT
1.	Photofrin/2/i.v.	Polypoid tumour (0.8 cm)	Whitish necrosis	Sloughing of tumour (100%)	Carcinoma	Microadenomas
2(i)	ALA/60/oral	Polypoid tumour (2.0 cm)	Whitish necrosis	No macroscopic change	DA + SD	DA + SD
(ii)	Photofrin/2/i.v. (3 months after ALA)	Polypoid tumour (2.0 cm)	Whitish necrosis	Sloughing of tumour (70%)	DA + SD	DA + MD
3.	Photofrin/2/i.v.	Polypoid tumour (1.6 cm)	Inflamed surface	Sloughing of tumour (40%)	DA + SD	DA + MD
4.	ALA/60/oral	Polypoid tumour (3.0 cm)	Whitish necrosis	No macroscopic change	DA	DA
5.	ALA/60/oral	Polypoid tumour (1.5 cm)	Whitish necrosis	Sloughing of tumour (20%)	DA	DA
6.	ALA/60/oral	Polypoid tumour (0.5 cm)	Whitish necrosis	No macroscopic change	RA	RA

DA, duodenal adenoma; SD, severe dysplasia; MD, moderate dysplasia; RA, rectal adenoma.

Figure 2. Histological section of biopsy from patient 4 taken 3 days after PDT. Superficial necrosis is seen with underlying viable glands.

have healed with mucosa that showed no more than mild dysplastic changes [30].

In conclusion, PDT looks a promising technique for treating polyps in familial adenomatous polyposis in situations where surgery is inappropriate. However, further work is required to optimise the choice of photosensitising drug and the dosimetry of both drug and light so as to obtain adequate polyp destruction with sound healing.

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