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The pharmacokinetics and safety of porfimer after repeated administration 30–45 days apart to patients undergoing photodynamic therapy

S. P. Pereira^{*}, L. Ayaru^{*}, R. Ackroyd[†], D. Mitton[†], G. Fullarton[‡], M. Zammit[‡], Z. Grzebieniak[§], H. Messmann[¶], M.-A. Ortner^{**}, L. Gao^{††}, M. M. Trinh^{‡‡}, and J. Spénard^{§§}

^{*}UCL Division of Surgery & Interventional Science, London, UK. [†]Royal Hallamshire Hospital, Sheffield, UK. [‡]Gartnavel General Hospital, Glasgow, UK. [§]II Katedra i Klinika Chirurgii Ogólnej i Onkologicznej, Wrocław, Poland. [¶]Clinic of Augsburg, Augsburg, Germany. ^{**}Division Gastro-Entérologie/Hépatologie, University Hospital Inselspital, Bern, Switzerland. ^{††}Formerly with Charles River Laboratory, Worcester, MA, USA. ^{‡‡}Pharsight Corporation, Montréal, QC, Canada. ^{§§}Axcan Pharma Inc., Mont-Saint-Hilaire, and Department Pharmacology, Faculty of Medicine, Université de Montréal, Montréal, QC, Canada.

SUMMARY

Background—Porfimer is an intravenous (i.v.) injectable photosensitizing agent used in the photodynamic treatment of tumours and of high-grade dysplasia in Barrett's oesophagus.

Aim—To assess the pharmacokinetics as well as the safety profiles of porfimer after a first and a second dose administered 30–45 days apart in patients undergoing photodynamic therapy.

Methods—Nineteen patients (16 with cholangiocarcinoma) were enrolled. Porfimer sodium was administered by i.v. injection over 3–5 min. Blood samples were collected prior to starting i.v. drug injection and postdose at different time points after the first and second administrations.

Results—Porfimer exposure values after the second administration were statistically higher than those observed after the first administration, suggesting a slight accumulation of porfimer following repeated administration. The apparent mean elimination half-life of porfimer increased from 410 h after the first administration to 725 h after the second administration. The safety profiles of porfimer after a first and a second administration were similar and did not raise additional concern. Eight patients experienced nine serious adverse events. Only photosensitivity was deemed study-drug related.

Conclusion—Porfimer appears to display a safe and tolerable profile when used in patients requiring a second photodynamic therapy within 45 days.

INTRODUCTION

Porfimer (Photofrin®, Axcan Pharma, Canada) is an intravenous (i.v.) injectable photosensitizing agent used in the photodynamic treatment (PDT) of tumours and of high-grade dysplasia (HGD) in Barrett's oesophagus (BO). Forty to fifty hours following the injection of the reconstituted freeze-dried product, the tumour or HGD is illuminated with a

630-nm wavelength laser light to induce the light- and oxygen-dependent cytotoxic and antitumour actions of porfimer.

The pharmacokinetic (PK) profile of porfimer has been previously assessed in four male cancer patients. After a 2-mg/kg dose of porfimer sodium, the mean $\pm$ standard deviation (s.d.) values of key serum PK parameters were as follows: peak serum concentration was $15 \pm 3 \mu\text{g/mL}$, the elimination half-life was $250 \pm 285 \text{ h}$, the steady-state volume of distribution was $0.49 \pm 0.28 \text{ L/kg}$ and the total serum clearance was $0.051 \pm 0.035 \text{ mL/min/kg}$. The mean $\pm$ s.d. serum concentration at 48 h was $2.6 \pm 0.4 \mu\text{g/mL}$.^{1, 2} Porfimer was approximately 90% protein-bound in human serum, studied *in vitro*. The binding was independent of concentration over the concentration range of 20–100 $\mu\text{g/mL}$.¹

The PK parameters of porfimer were also studied in 24 healthy subjects (12 men and 12 women) who received a single dose of 2 mg/kg porfimer sodium given via the i.v. route.² The serum decay was bi-exponential, with a slow distribution phase and a very long elimination phase. The mean $\pm$ s.d. beta (β) elimination half-life was $415 \pm 104 \text{ h}$ ($17 \pm 4.3 \text{ days}$). The mean $\pm$ s.d. values for peak serum concentration (C_{max}) was $40 \pm 11.6 \mu\text{g/mL}$ and for $AUC_{0-\infty}$ was $2400 \pm 552 \mu\text{g h/mL}$ and did not differ between men and women.

In some patients with large tumours, a second administration of porfimer may be indicated. However, as porfimer has a long elimination half-life (only about 71% of the dose is eliminated from the body in 30 days),² there is a possibility that the second injection may result in drug accumulation. In this study, we assessed the PK profile of porfimer after a first and second dose administered 30–45 days apart in patients undergoing PDT therapy. As a secondary objective, we also evaluated the safety of porfimer after both a first and second administration in the study population.

METHODS

Patients

The study population consisted of 19 male or nonpregnant female patients aged between 18 and 75 years who were scheduled to undergo PDT with porfimer and who met the following inclusion criteria: (i) likely to receive a second course of PDT in the coming 30–45 days, according to the investigator's judgment based on the patient's clinical condition and/or medical history; (ii) free of any conditions that may alter distribution or elimination of drugs, including, but not limited to, renal failure, liver failure and previous cholecystectomy; and (iii) legally able to provide a written informed consent.

Exclusion criteria were: (i) a previous administration of porfimer in the 120 days preceding study day 1; (ii) female patients who were pregnant or breast-feeding; (iii) a known hypersensitivity to porphyrins or sunlight, porphyria or clinically significant abnormal serum creatinine as determined by the investigator; (iv) HIV, hepatitis, or other blood-transmissible disease; and (v) patients unable to return for all required follow-up visits or those with inadequate venous access or with a significant history of fainting when undergoing blood withdrawal.

All patients signed the informed consent prior to their participation in the study. The study protocol and all other relevant documents were reviewed and approved by the institutional review board at each participating centre. The study was conducted in accordance with International Conference on Harmonization and Good Clinical Practice guidelines and the Declaration of Helsinki. The guidelines also met the US Code of Federal Regulations (Title 21, Part 56) and the Tri-Council Policy Statement (Canada).

Study design

This study was an open-label, single-arm, multicentre design. Patients likely to need repeated administration of porfimer for PDT within 30–45 days were included. Porfimer sodium (Photofrin®, Axcan Pharma, Canada) was administered by i.v. injection 2 mg/kg over 3–5 min. Venous blood samples (7–10 mL) were collected prior to starting i.v. injection of porfimer and post-dose at 5 min, 1, 12, 24, 48 and 72 h, 5, 8, 15, 22, 29 and 36 days (if a second administration had not occurred between days 30 and 36). If indicated for treatment, a second porfimer sodium 2 mg/kg dose was administered between 30 and 45 days after the first dose and blood was sampled at the same time points as after the first administration.

Sample assays

Blood samples were collected in tubes without anticoagulant and allowed to clot at room temperature for at least 30 min. After centrifugation, serum was harvested and stored at -70°C or lower pending analysis by the central laboratory (Charles River Worcester, MA, USA). The assay used was based on a published method by Bellnier *et al.*³ Briefly, the method consisted of quantifying total monomeric porphyrins by spectrofluorometry after hydrolysis of porfimer oligomers under red light. Excitation and emission fluorescence were set at 404 nm and 627 nm respectively. The dynamic range of the assay was 60–3000 ng/mL. Accuracy, as measured by bias, ranged between -7.3% and -1.2% across concentrations and analytical runs. Precision, as measured by coefficient of variation (CV), ranged from 6.1% to 11.9% across concentrations and analytical runs. Porfimer is composed of oligomers of various molecular weights that are formed from three monomer units, 2,4-(4,2)-hydroxyethyl-vinyl deuteroporphyrin IX, haematoporphyrin IX and protoporphyrin IX (all three similar fluorescence properties). There are residual levels of monomers in each batch of porfimer finished product and reference standard. Thus, serum porfimer concentrations were analysed using two standard curves for the quantification of porfimer levels in human serum samples. One standard curve (uncorrected) represented fluorescence response for the porfimer product, including levels of monomers. Another standard curve (monomer-corrected) was corrected to represent oligomer only by subtracting response of monomers present. Based on information on metabolism of porfimer, human samples collected within 1 h after injection were quantified with the uncorrected curve and samples collected more than 1 h post-injection were quantified with the monomer-corrected curve. Calculated concentrations for all samples were expressed in ng/mL.

Pharmacokinetic analyses

Pharmacokinetic parameters of porfimer in serum after the first and second administrations were calculated by compartmental and noncompartmental PK analysis methods for all subjects who completed at least one phase of the study (PK evaluable population). For the compartmental PK analysis, multiple compartmental models were tested and the best model was selected based on standard diagnostics (e.g. Akaike information criteria) and by looking at pertinent graphical representations of goodness-of-fit (e.g. fitted and observed concentrations vs. time, weighted residuals vs. time). Noncompartmental PK parameters (e.g., $AUC_{0-\text{last}}$, C_{max} , T_{max} , $t_{1/2}$) were derived using a validated version of WinNonlin (Enterprise v 5.2, Pharsight®, St. Louis, MO, USA) and compartmental PK parameters ($t_{1/2\alpha}$, $t_{1/2\beta}$, $t_{1/2\gamma}$) were derived using NONMEM version VI. Relationships between PK parameters and demographic covariates (e.g. body weight, age and height) were explored.

Safety analysis

All subjects who received at least one administration of study drug were to be included in the safety analysis.

Statistical analysis

Individual concentrations and PK parameters of serum porfimer in the PK-evaluable population were summarized with descriptive statistics, after the first and second administrations, for all subjects combined and by gender. The median, minimum and maximum were presented for $T_{\max}$.

A two-sided paired *t*-test (5% significance level) was performed on select PK parameters after the first and second administrations to assess the extent of accumulation of porfimer and the effect of gender on porfimer exposure. Descriptive statistics were performed on adverse events (AEs).

RESULTS

Patients' demographics and disposition

Nineteen patients (9 men and 10 women) were enrolled into the study and constituted the safety population. All were Caucasians with a mean (s.d.) age of 66.0 (10.2) years. Subjects' demographic data are summarized in Table 1. The main indications for PDT were bile duct cancer in 84.2% (16/19) and oesophageal cancer in 15.8% (three of 19) of patients. Fourteen of the 19 participants received both porfimer administrations. Nine patients completed all the study procedures and four patients completed all visits, but did not complete all the required procedures. Five patients terminated early from the study because of AEs; four of these five patients died and one withdrew from the study due to worsening of his/her medical condition. These patients are described in more detail in the safety results section.

Baseline liver function tests were available for 15 of the 16 subjects with cholangiocarcinoma. Mean (s.d., range) alkaline phosphatase, ALT and bilirubin were 452.4 (33.6, 87–1163) U/L, 61.6 (32.7, 25–138) U/L and 42.3 (31.2, 6–111) $\mu\text{mol/L}$ respectively for all subjects with cholangiocarcinoma. Thirteen, 10 and 11 subjects had abnormal alkaline phosphatase, ALT and bilirubin levels at entry respectively.

Pharmacokinetics results

Of the 19 patients enrolled into the study, a total of 18 patients (8 men and 10 women) constituted the PK evaluable population. One patient had only eight blood collections following the first porfimer dose and died thereafter, leaving a non-evaluable PK profile. All patients included in the PK evaluable population displayed porfimer predose serum concentrations above the lower limit of quantification (LOQ). Individual endogenous predose concentrations represented <2.7% of the corresponding $C_{\max}$ observed after each porfimer administration. As a result, predose concentration values were deemed as not interfering with the PK analysis.

Porfimer serum concentrations declined in a multi-exponential manner after the first and second administrations as shown in Figure 1. Serum concentrations were more than 10-fold higher than the LOQ at 29 days postdose following both the first and the second porfimer administrations.

Mean (s.d.) serum PK parameters of porfimer following i.v. injection of two doses of 2 mg/kg porfimer sodium 30–45 days apart [mean (s.d., range) = 36 (4.4, 30–44) days] are summarized in Table 2. Overall, porfimer exposure values after the second administration were 14.7% and 34.0% higher for $AUC_{0-\text{last}}$ ($P = 0.0378$) and $AUC_{0-\infty}$ ($P = 0.0002$) respectively than those observed after the first administration, as shown in Table 3. The apparent mean elimination half-life of porfimer appeared to increase after the second administration (from 410 h after the first administration to 725 h). No statistically significant difference was observed for $C_{\max}$.

between the second and the first administrations. Patients who received both administrations had 20.7%–48.2% of the AUC extrapolated to infinity after the AUC_{0-last} .

Distribution and elimination half-life ($t_{1/2}$) values of porfimer were derived using a three-compartment open model. The PK profiles of porfimer after the first and second administration were characterized by a very rapid alpha (α) distribution phase, a slower β elimination phase and a very long gamma (γ) elimination phase. Mean (s.d.) for the $t_{1/2\alpha}$, $t_{1/2\beta}$ and $t_{1/2\gamma}$ are summarized in Table 4. Following the first administration, mean $t_{1/2\alpha}$ was 0.0346 h (2.08 min), mean $t_{1/2\beta}$ was 19.8 h and mean $t_{1/2\gamma}$ was 310 h (12.9 days). For the second administration, mean $t_{1/2\alpha}$, $t_{1/2\beta}$ and $t_{1/2\gamma}$ of porfimer were 31%, 11.2% and 21% higher than those observed after the first administration.

A posteriori stratification by gender was performed to assess the effect of gender on the PK of porfimer. The PK evaluable population included ten women and eight men for the first administration and eight women and six men for the second administration. Porfimer exposure parameters in women were 6.9%, 12.7% and 14.8% higher (C_{max} , AUC_{0-last} and $AUC_{0-\infty}$ respectively) than those observed in men after the first administration. Following the second administration, these values were comparable between women and men. Mean $t_{1/2\beta}$ and $t_{1/2\gamma}$ in women were slightly higher than those observed in men (increases ranged from 7.5% to 15.3%) following both the first and the second porfimer administrations. However, gender differences in porfimer exposure were not statistically significant for the first and second administrations of porfimer as assessed by the two-sided paired *t*-test.

Relationships between C_{max} , AUC_{0-last} and $AUC_{0-\infty}$ and demographic covariates (e.g. body weight, age and height) were explored. No correlation was observed between any of these PK parameters and age or height. A negative correlation between AUC_{0-last} , $AUC_{0-\infty}$ and weight was observed.

Safety results

Seventeen of the 19 enrolled patients reported a total of 65 AEs. Overall, AEs most frequently reported by system organ classes were photosensitivity reactions (five of 19), procedural pain (five of 19), abdominal pain (four of 19), cholangitis (four of 19), constipation (four of 19), nausea (four of 19), postprocedural complication (three of 19), malignant neoplasm progression (three of 19), erythema (three of 19), lethargy (two of 19) and procedural nausea (two of 19). Nausea was reported by three of 14 patients (21.4%) after the second porfimer administration as compared with one of 19 patient (5.3%) after the first. Procedural pain was reported by four of 19 patients (21.1%) after the first porfimer administration and by five of 14 patients (35.7%) after the second. However, these differences were not statistically significant.

A total of eight patients experienced nine AEs considered to be related to study drug, four patients (five events) after the first administration and four patients (four events) after the second. All these treatment-related AEs were observed in the class of ‘skin and subcutaneous tissues disorders’ and were mild or moderate in intensity.

The number of subjects reporting AEs was similarly distributed between the first and second administrations of porfimer, with 16/19 patients (84.2%) reporting at least one AE after the first porfimer administration and 11/14 patients (78.6%) after the second. Most of the reported AEs were moderate in intensity. Only three patients reported severe AEs after the first administration of porfimer. After the first porfimer administration, only one subject reported an AE leading to early discontinuation.

A total of eight patients experienced nine serious AEs (SAEs), eight SAEs after the first porfimer administration and one after the second. Four patients died during the study prior to

receiving the second porfimer administration. Three of the patients died of disease progression (three SAEs) and one patient died as a consequence of a cardiac arrest (one SAE). The other nonfatal SAEs requiring hospitalization or prolongation of hospitalization were cholangitis (three SAEs), dehydration (one SAE) and photosensitivity (one SAE). From all SAEs reported in the study, only photosensitivity was deemed by the investigators as related to the study drug.

There were no laboratory AEs recorded in this study. Overall, biochemistry and haematology results different from baseline were observed during the study, but none was considered clinically meaningful or classified as treatment-related. Individual biochemistry and haematology parameters did not exhibit clinically significant differences between the first and second administration of porfimer. Overall, vital signs remained stable throughout the study period.

DISCUSSION

Porfimer based PDT is a treatment option for many tumours such as cholangiocarcinoma⁴ and HGD in BO.^{5–7} In some patients, a second course of treatment may be needed and therefore the primary objective of this study was to assess the PK profile of porfimer after a first and a second 2 mg/kg dose administered 30–45 days apart. The secondary objective was to document the safety of porfimer after the first and second administration.

Pharmacokinetic parameters $AUC_{0-\infty}$, C_{max} and $t_{1/2}$ were consistent with those previously observed (Data on file, Axcan Pharma1). The PK parameters of porfimer were also evaluated using compartmental methods. Although serum concentrations of porfimer were previously fitted using a two-compartment model in the literature, data from the current study were best characterized using a three-compartment model. This is consistent with our knowledge of an extensive distribution of porfimer in deep compartments such as skin, muscles and fat (Data on file; Axcan Pharma). Tissue distribution studies measuring porfimer in normal and malignant tissues, removed during surgical debulking following i.v. administration to patients with recurrent peritoneal carcinomatosis or sarcomatosis, showed similar distribution of porfimer in skin, fat and muscles.⁸ Based on the three-compartment model, a very rapid $t_{1/2}$ distribution of approximately 2.1 min was observed, followed by a $t_{1/2\beta}$ of approximately 20 h and by a very slow terminal $t_{1/2\gamma}$ of 13–15 days. Although a statistically significant increase in total exposure parameters was observed following the second administration of porfimer, the increase in AUC_{0-last} after the second administration was of low magnitude (14.7%), suggesting a low extent of accumulation of the drug. A more important increase with the second administration was noted for $AUC_{0-\infty}$ (34%) and this was associated with a substantial prolongation of the apparent elimination half-life (725 h for the second administration vs. 410 h for the first administration). These results should be interpreted with caution as after the second administration, more than 20% (20.7–48.2%) of the $AUC_{0-\infty}$ was extrapolated compared with the AUC_{0-last} and therefore the estimation of the apparent elimination half-life may be inaccurate. Compared with the first administration, results of the compartmental analysis showed only a slight prolongation of 21% of the terminal $t_{1/2\gamma}$ after the second administration. The negative correlation between total systemic exposure and weight supports the hypothesis of porfimer distribution into a deep compartment represented by skin, muscles and possibly fat. As previously reported, women tended to have a higher porfimer exposure than men.² This difference might be explained by the differences in weight between male and female subjects. Overall, the minor accumulation of porfimer following repeated dosing did not display gender-specific trends.

It is of interest to note that very low predose concentrations levels of porfimer were observed in all patients. All predose concentrations corresponded to <2.7% of the peak porfimer serum concentration for each patient and were not likely to affect the PK analysis of porfimer in the

current study. These predose levels of porfimer may be due to potential interferences with endogenous porphyrins measured with the fluorescence assay.

The safety profiles of porfimer following the first and second administrations were similar. The most frequently reported AEs by system organ classes were photosensitivity reaction, procedural pain, abdominal pain, cholangitis, constipation, nausea, postprocedural complication, malignant neoplasm progression, erythema, lethargy and procedural nausea. All the observed treatment-related AEs were observed in the class of skin and subcutaneous tissues disorders (eight events). From all SAEs reported in the study, only photosensitivity was interpreted by the investigator as related to the study drug.

In conclusion, the PK profile of porfimer after a second administration 30–45 days after a first administration showed some differences indicative of slight porfimer accumulation in the body. However, this drug accumulation did not raise safety concerns as the observed AEs were not significantly different from those observed after a first administration. There also appeared to be gender differences in the PK profile of porfimer after the first and second administrations. However, these differences were not statistically significant and do not warrant porfimer sodium dose adjustment based on gender.

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REFERENCES

1. Axcan, Pharma. Photofrin (R) Official Product Monograph. Axcan Pharma Inc.; Mont-Saint-Hilaire, QC: 2005.
2. Houle JM, Clervois N, Bain S, Spenard J. Lack of effect of sex and disease state on the pharmacokinetics of porfimer sodium. *Clin Pharmacokinet* 2006;45:923–30. [PubMed: 16928153]
3. Bellnier DA, Dougherty TJ. A preliminary pharmacokinetic study of intravenous Photofrin in patients. *J Clin Laser Med Surg* 1996;14:311–4. [PubMed: 9612197]
4. Ortner MA, Dorta G. Technology insight: photodynamic therapy for cholangio-carcinoma. *Nat Clin Pract Gastroenterol Hepatol* 2006;3:459–67. [PubMed: 16883350]
5. Overholt BF, Wang KK, Burdick JS, et al. Five-year efficacy and safety of photodynamic therapy with Photofrin in Barrett's high-grade dysplasia. *Gastrointest Endosc* 2007;66:460–8. [PubMed: 17643436]
6. Overholt BF, Panjehpour M, Halberg DL. Photodynamic therapy for Barrett's esophagus with dysplasia and/or early stage carcinoma: long-term results. *Gastrointest Endosc* 2003;58:183–8. [PubMed: 12872083]
7. Overholt BF, Panjehpour M, Haydek JM. Photodynamic therapy for Barrett's esophagus: follow-up in 100 patients. *Gastrointest Endosc* 1999;49:1–7. [PubMed: 9869715]
8. Hahn SM, Putt ME, Metz J, et al. Photofrin uptake in the tumor and normal tissues of patients receiving intraperitoneal photodynamic therapy. *Clin Cancer Res* 2006;12:5464–70. [PubMed: 17000681]

Figure 1.
Serum concentration of porfimer following 2 mg/kg i.v. injection administered on two different occasions 30–45 days apart.

Table 1

Demographic characteristics of the patient population

Demographic variable	Porfimer (<i>n</i> = 19)
Mean age (s.d.), years	66.0 (10.24)
Check-in weight (s.d.), kg	76.6 (18.81)
Height (s.d.), cm	168.2 (13.69)
Gender, <i>n</i> (%)	
Male	9 (47.4)
Female	10 (52.6)
Race, <i>n</i> (%)	
Caucasian	19 (100)
Indication for PDT, <i>n</i> (%)	
Oesophageal cancer	3 (15.8)
Bile duct cancer	16 (84.2)

Table 2

Mean (s.d.) pharmacokinetic parameters of porfimer calculated using noncompartmental analysis

Parameters	First administration (<i>n</i> = 18)	Second administration (<i>n</i> = 14)
AUC_{0-last} (ng h/mL)	2 309 369.6 (477 045.85)	2 649 241.6 (416 035.71)
$AUC_{0-\infty}$ (ng h/mL)	2 937 444.7 (627 338.34)*	3 937 582.7 (1 034 343.21) [†]
$AUC_{0-last}/AUC_{0-\infty}$	0.859	0.693
C_{max} (ng/mL)	43 105.6 (10 466.33)	41 307.1 (8737.85)
T_{max} (h) [‡]	0.183 (0.117-1.733)	0.175 (0.130-1.283)
$t_{1/2}$ (h)	409.9 (154.43)*	725.0 (223.91) [‡]

Values represent arithmetic mean (s.d.).

* *n* = 14 (Three subjects withdrew early due to adverse events, one subject did not display a linear terminal porfimer serum profile).[†] *n* = 13 (One subject did not display a linear terminal serum profile).[‡] Median (min, max).

Table 3

Comparison of dose-normalized porfimer pharmacokinetic parameters following the first and second administrations

First/second porfimer administration	Mean difference (second – first)	95% Confidence interval of mean difference	<i>P</i> -value*
$AUC_{0-last}/dose$	1750.87	114.66 to 3387.07	0.0378
$AUC_{0-inf}/dose$	7579.632	4509.31 to 10 649.95	0.0002
$C_{max}/dose$	-5.7	-34.54284 to 23.10709	0.6753

* Two-sided paired *t*-test.

Table 4

Mean (s.d.) pharmacokinetic parameters of porfimer calculated using compartmental analysis

Parameters (h)	First administration (n = 18)	Second administration (n = 14)
$t_{1/2} \alpha$	0.0346 (153) (2.08 min)	0.0453 (160) (2.72 min)
$t_{1/2} \beta$	19.8 (22.9)	21.9 (15.0)
$t_{1/2} \gamma$	310 (25.9) (12.9 days)	375 (14.3) (15.6 days)