Cellular and Molecular Biology ™ **55**, N°1, 84-97
DOI 10.1170/T841

ISSN 1165-158X
2009 Cell. Mol. Biol.™

A SYSTEMATIC REVIEW OF TREATMENT OPTIONS FOR DERMAL PHOTOSENSITIVITY IN ERYTHROPOIETIC PROTOPORPHYRIA

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Received December 31th, 2008; Accepted January 17th, 2009; Published February 16th, 2009

Abstract – Erythropoietic protoporphyria (EPP) is a rare inherited disease characterized by dermal photosensitivity due to the accumulation of photosensitizer protoporphyrin IX. We performed a systematic database search on studies related to treatment of EPP. A total of 25 relevant studies were retrieved, 16 of them dealing with the application of beta-carotene. Two studies were found on each of the three substances, n-acetyl-cysteine (NAC), cysteine, and dihydroxyacetone/Lawson (henna). In addition, single studies on vitamin C, canthaxanthin and UVB treatment respectively, were located. The total number of patients in the 25 studies was 454, including 337 patients in the various beta-carotene trials. Most studies were published in the 1970's. Efficacy criteria were not standardized. Only 5 of the 25 studies were randomized and controlled trials; the rest were either open-label, uncontrolled studies or retrospective case reports. Four of the five well-designed studies suggested lack of efficacy of beta-carotene, NAC and vitamin C. The results of the beta-carotene studies were strongly contradictory and efficacy was inversely correlated with study quality. Our data confirm the opinion of experts in the field who are much more skeptical as to its efficacy than were early proponents of treatment with this agent. We conclude, that the available data are insufficient to prove efficacy of any treatments studied so far in EPP. We emphasize the necessity of high quality efficacy studies in porphyrias and in other rare diseases.

Key words: Erythropoietic protoporphyria, evidence-based treatment, beta-carotene.

INTRODUCTION

Erythropoietic protoporphyria (EPP), an inborn error of heme biosynthesis with an estimated prevalence of 1: 150'000 in the European populations, is due to a partial deficiency of the enzyme ferrochelatase (FECH) (30). The symptoms are elicited by accumulation of the FECH substrate protoporphyrin IX (PPIX) which acts as a photosensitizer in light exposed skin areas.

The initial clinical symptom of EPP is skin pain of tingling, stinging and burning character arising immediately or within a few minutes of sun light exposure (41). After a prolonged sunlight irradiation, phototoxic reaction develops which results in an intolerable pain without visible skin changes in less severe attacks. The pain can also be accompanied by various other symptoms including erythema, edema, wheals, lesions or petechia. The back of hands, perioral region, back of nose and upper edges of ears are the most frequently affected areas. The EPP symptoms may last for several days causing severe incapability.

Apart from bone marrow transplantation, so far, no treatments to either increase FECH activities or to decrease PPIX accumulation are available (36). Gene therapy or stem cell therapy to replace defective enzyme was successfully tested in animal models only (12,35,38,39). Instead, the current treatment modalities are aimed at minimizing PPIX's pathogenic effects by way of: *(1)* increasing skin coloration to block sun light activation of PPIX and *(2)* increasing the levels of antioxidants to scavenge radicals and other secondarily formed reactive molecules.

Although multiple treatment options were proposed, many of them have only been applied in single patients. Nevertheless, an effective treatment strategy for EPP has been a topic of

discussion in the medical literature for many years (9,13,31,43,45).

To acquire an in-depth view on this subject, we performed a systematic review on different treatment modalities.

METHODS

Search Strategies

In order to select appropriate studies, we used the MESH terms "porphyria/drugs treatment", "porphyria/diet treatment", porphyrias / mortality" and "porphyrias / prevention and control" in the PubMed-database. The term "porphyria" rather than "protoporphyria" was used, as EPP was subsumed in the term porphyria up to 2004. References given in the review articles on additional EPP treatment studies were checked for further publications.

Eligibility Criteria

Articles with only summarized statements on treatment effects, case reports involving less than 3 patients, treatment of EPP related liver disease and animal studies were excluded. However, due to the orphan status of the disease and the scarcity of the studies, the term "study" was applied broadly in our compilation with the intention to include all data that are relevant to the subject. Care was taken to exclude studies on identical patients or patient cohorts. Under such circumstance, the most recent study or alternatively, the study with the most detailed information, was selected.

Assessment of Methodological Quality

Retrospective data collections were categorized as "case series"; prospective data collections without a control regimen as "uncontrolled trials"; and prospective data with random allocation to both active and control as "controlled trials". A purpose defined form for data extraction was developed. The following information concerning methodological quality was extracted.

(1) Patient selection and/or PPIX levels reported and compatible with diagnosis, *(2)* study protocol defined prior to study begin, *(3)* drug dosage defined prior to study begin including dosage adjustment according to a priori and explicitly defined criteria, *(4)* quantitative efficacy assessment by criteria defined prior to study begin, *(5)* efficacy assessment by structured tool (e.g. diary, questionnaire, phototesting), *(6)* baseline assessment prior to study begin, *(7)* control of seasonal effects/weather, *(8)* duration of study defined prior to study begin, *(9)* control group, *(10)* randomisation, *(11)* blinding of investigators, *(12)* drop-out rates reported, *(13)* results on all apriori defined efficacy criteria published. The quality scores were assigned independently by two investigators (X.S., E.I.M.) with the exception of the French study (10) that was only judged by E.I.M. Discrepancy among the scores was discussed and consensus was subsequently reached. The number of fulfilled quality criteria of a trial divided by the total number of criteria was used as quality score resulting in a score between zero and one.

Therapeutic endpoints

Measurement of efficacy in EPP is difficult (24). A generally accepted method does not exist. We listed the different efficacy endpoints used in the studies and the methods for their assessment.

Data extraction

Data from single patients were retrieved from the original publications whenever possible. Data were converted to SI units using a molecular weight 562 for PPIX. In order to combine quantitative and qualitative results, a relative increase of light tolerance by a factor 3 was considered as moderate, and by a factor 5 as strong improvement in accordance with the literature (25,26). Efficacy was calculated as the fraction of patients having moderate or strong improvement. As variable dosages were applied in single study, the mean of dosage range in each study was correlated to efficacy.

Funding of the studies

The role of funding was not considered, because of the lack of information in most of the studies.

RESULTS

In October 2006, we selected a total of 774 articles from the database "PubMed" using the above mentioned search terms. Among them, 133 articles, of which the treatment of EPP could not be excluded as subject based on the title, were manually selected. Subsequently, original studies on treatment of EPP skin symptoms in English, German and French languages published between 1972 and 2006 were analyzed. The selection of publications was complemented by references cited in selected articles. An additional search in May 2008 did not obtain new data.

From a total of 25 relevant clinical studies, 16 studies were on the subject of efficacy of betacarotene (2, 3, 4, 8, 10, 16, 19, 21, 22, 26, 27, 32,44,46,47,48), two on the efficacy of N-acetylcysteine (NAC)(5,33), cysteine (28,29) and of topical application of dihydroxyacetone (DHA)/Lawson (henna) (14,15,37), respectively (table 1). Single studies on canthaxanthin (11), vitamin C (6) and ultraviolet B irradiation (UVB) were available (7). Totally, 454 patients were included in all trials. However, treatment efficacy was often not the main topic of the publications.

Assessment of efficacy in EPP

If efficacy was assessed by more than one method, primary and secondary endpoints were never defined (table 1). Efficacy assessments were either patient's quantitatively reported sunlight tolerance time (6 studies (4, 8, 26, 27, 28 ,29)), intensity of phototoxic symptoms (2 studies (14,37)), time to provoke symptoms by artificial or natural light (6 studies (3, 6, 14, 22, 27,37)) or improvement of symptoms (18 studies (2, 3, 4, 5, 6, 7, 10, 11, 16, 19, 21, 22, 32, 33, 44, 46,47,48)). Data on sunlight tolerance or phototoxic symptoms were collected from patients' dairies (4 trials (2,8,28,29)), from

retrospective questionnaires (5 studies (11, 26, 27,28,33)) or from standardized or open questions (15 studies (3, 4, 5, 6, 7, 10, 16, 19, 21, 22,32,44,46,47,48)). Two studies applied a visual analog scale (VAS) (6,33). All these different methods were combined under the heading "EPP symptoms" in the tables 2b, 3 and 4.

Phototesting was either performed by determination of the irradiation threshold for minimal erythemal dose (MED, 2 studies (5,48)) or of the time required to provoke minimal erythema (TME, 2 studies (26,29)). As an artificial provocation, white light or lights with specific wavelengths selected by monochromators were applied. In two studies, symptoms were provoked by exposure to natural sunlight.

Beta-carotene

Sixteen studies on treatment efficacy of beta-carotene were published between 1972 and 1996. A total of 337 patients were treated including 12 “case series”, three “uncontrolled trials” and one “cross-over controlled trial” (Table 2a & b).

As efficacy endpoints, change of either subjective symptoms or sunlight tolerance was used in 15 studies, reactivity in phototesting in two studies. Eighteen percent of the patients had no improvement in symptoms, 28 % had moderate and 54 % had strong improvement. Results of phototesting showed no effect in 29 %, moderate effect in 56 % and strong effect in 15 % of the patients, respectively. The only randomized, controlled study (8) showed no or negative effect on “exposure time to bright sunlight” in 9 of the 11 studied patients (82 %). A moderate and a strong effect were observed in the two remaining patients (18%), respectively. Among all patients of this study, the mean exposure time increased from 27 to 40 min per day. However, this small but yet statistically significant improvement was viewed as clinically irrelevant by the authors since no effect was found in the other two efficacy assessments i.e., "symptom score" and "hours out of doors".

Study qualities

Patient selection (table 2a): In two studies, the EPP diagnosis was based on typical symptoms and increased erythrocytic PPIX concentrations. In two other studies patients were only described as suffering from EPP with no additional clinical criteria provided. In those 9 studies in which numeric data were available, the means of PPIX concentrations in the trials ranged between 10 and 23 µmol/L, and the values of single patients ranged between 2.1 and 75 µmol/L. The documented PPIX concentrations although sufficient to establish the diagnosis of EPP overlaps in the lower range with those found in iron deficiency or lead intoxication. Two studies provided no information on diagnostic criteria for patient selection.

The dosage of beta-carotene varied both within and among studies ranging from 25 mg to 300 mg/day. Lower dosages were used in children, and in adults in the early studies as well (19,22). Doses between 100 and 300 mg/day were applied to adults in the more recent studies.

Study Duration was variable and not pre-defined in all but two studies.

Allocation, performance and detection: As 15 of the 16 studies did not have a control group, neither random allocation, nor prevention of the bias of performance, nor detection bias were applicable. Detection bias was not specially cared for in the only controlled trial because the effect of skin coloring under beta-carotene prevented blinding of investigators.

Study quality or dose versus efficacy: In order to test whether the study quality has any impact on efficacy reported, we plotted quality scores of the studies versus their efficacies (figure 1A) An inverse correlation resulted ($r=-0.63$, $p=0.019$, $n=16$). Efficacy was not correlated to the dosage ($r= 0.11$, $p=0.70$, figure 1B)

Cysteine/N-acetyl cysteine (table 3):

Cysteine was reported to be effective in a double blind, placebo controlled study (29), both with regard to phototesting (protection factor 2.3 ± 1.03) and subjective assessment of sunlight exposure time until symptoms develop (protection factor all daylight data: 1.48 ± 0.79, and 1.33 ± 0.66 for exposure between 11.00 to 15.00h). Concurrently, the mean time of sunlight tolerance increased from 58 min to 70 min of exposure during daytime and from 44 min to 52 min of exposure between 11.00 to 15.00h. A single blinded controlled follow-up study apparently confirmed the positive effect of cysteine (28). As all participants of this study received placebo during the first study period in June or July, no randomization and no control for seasonal effects of sunlight intolerance were conducted. Only the participants, but not the

Table1. Efficacy endpoints and assessment methods

First Author	Year	Treatment	Efficacy endpoints	Assessment method
Baart	1972	betacarotene	maximum exposure time to sunlight which the patients could endure without difficulties	"Diary": Regular recording maximum exposure time to sunlight, baseline retrospective
Lewis	1972	betacarotene	not explicitly formulated (graded improvement, sunlight exposure until development of symptoms)	retrospective open questions (method not mentioned exactely)
Krook	1974	betacarotene	not explicitly formulated (skin symptoms (graded), patient satisfaction)	retrospective open questions on sunlight tolerance
Mathews	1974	betacarotene	sunlight tolerance, TME	(1) retrospective questionnaires (2) TME
Fusaro	1975	dihydroxy-acetone	minimal amount of sunlight exposure between 10.00h an14.00h that caused inflammatory reaction	patients exposed to sunlight before and during therapy
Beckert E	1976	betacarotene	sunlight tolerance ("Sonnentoleranz")	retrospective open questions on sunlight tolerance
Rice E	1976	dihydroxy-acetone/ Lawson	amount of time during midday sunlight exposure that is necessary to induce symptoms	patients exposed to sunlight before and during therapy
Corbett	1977	betacarotene	intensity of EPP symptoms, hours out doors(&hours in bright sunlight)	diaries
Goerz G	1977	betacarotene	not explicitly formulated (graded improvement)	retrospective open questions (subjective observations)
Mathews	1977	betacarotene	number of minutes of summer sunlight tolerated without the development of symptoms	(1) tolerance to sunlight by retrospective questionnaires (2) calculated from these data: protection index
Zaynoun	1977	betacarotene	clinical assessment of alterations of pain, discomfort and swelling and noting the length of time for symptoms and/or signs to appear in bright direct sunlight or diffuse daylight, phototesting at 400, 415 and 430 nm (MED)	(1) retrospective open questions (subjective observations) (2) phototesting
Eales	1978	canthaxanthin	patients' own evaluation of improved tolerance to the midday summer sun	questionnaire (?)
Niebauer	1978	betacarotene	not explicitly formulated (graded improvement)	retrospective open questions on sunlight tolerance
Thomsen	1979	betacarotene	period of time possible to stay in the sun	retrospective open questions on sunlight tolerance
Wennersten	1980	betacarotene	degree of reduction of clinical lesions and ability to turn to a fairly normal life	retrospective questions: 4 point scale (1=less than 25% reduction of symptoms, 2=25-50% reduction, 3=50-75% reduction, 4=75-100% reduction

First Author	Year	Treatment	Efficacy endpoints	Assessment method
Barth	1984	betacarotene	prolongation of time outdoor until development of skin alterations	retrospective open questions on sunlight tolerance
Crosby	1988	betacarotene	improvement of phototoxic reactions	retrospective open questions
De Sélys	1988	betacarotene/ canthaxatin	improvement of symptoms	retrospective open questions
Lehmann	1991	betacarotene	not explicitly formulated (sunlight tolerance, graded)	retrospective open questions on sunlight tolerance
Bijlmer-Iest	1993	NAC	estimation of time patient could tolerate exposure and compare to photosensitivity in normal life, duration of signs of photodermatosis, MED (405, 546 and "white" light).	questions (standardized?), phototesting
Mathews	1994	Cysteine	TME, length of sunlight exposure to develop symptoms of photosensitivity	phototesting, diaries
Collins	1995	UVB	all patients were questioned in October to assess overall effect. Especially they were asked the duration of benefit and the hours of direct sunlight they had been able to tolerate	retrospective standardized questions (?)
Norris	1995	NAC	VAS for itching, pain, redness, swelling; overall assessment	standardized questionnaire during treatment/placebo
Boffa	1996	Vitamin C	VAS for maximal improvement (+5), no change (0), maximal deterioration (-5) of sunlight tolerance compared to baseline; choice of treatment period with least photosensitivity.	standardized questions (?), VAS
Laar	1996	betacarotene	not explicitly formulated (graded improvement)	retrospective open questions (method not mentioned exactly)
Mathews	2002	cysteine	sun light tolerance, length of sunlight exposure and phototoxic symptoms, TME	questionnaire, diaries, phototesting

Table 2. Betacarotene studies:
2a: study design and patient selection:

	study design:	Dosage (in mg/d)	minimal b-carotene serum concentration[1)]	duration of study	Patient selection	PPIX in red cells mean ± SD µmol/L	range µmol/L
Lewis 1972	b-carotene only	50-75	204 µg/100ml	variable (1 year?)	not reported	20.2 ± 12.5	2.4 -29.5
Baart 1972	b-carotene only	25-125 (2 preparations hospital-pharmacy made and Roche, hospital-pharmacy prep was instable)	160 µg/100ml (Roche); 5 µg/100ml hospital pharmacy-made	5 months	not reported	not reported	not reported
Mathews 1974	b-carotene only	variable, mainly 120-180 up to 300 in adults, increase until effective	213-1234 µg/100ml	5 months to 3 years	Clinical signs, elevated levels of PPIX in red blood cells and feces	13.48±7.59	3.4 - 43.6
Krook 1974	b-carotene only	variable 75-200 ; total dose 9-60 g	no exact concentrations given; from graphs > 400µg/dl during therapy	4-15.5 months	not reported	only in graphs	only in graphs
Beckert 1976	b-carotene only	variable, 25-100	not determined	19-48 months	not reported	10.36 ± 11.89	2.10 - 30.04
Goerz 1977	b-carotene only	not indicated	(5390)7320±2400 µg/L	15-51 months	not reported	19.71 ± 9.69	11.48 - 41.69
Zaynoun 1977	b-carotene only (uncontrolled, retrospective)	75-200 in adults	>10µmol/L(>5370 µg/L)	Study period 5 years, time span of treatment not indicated	not reported	13.27 ± 6.27	4.9 - 23.7
Corbett 1977	beta carotene vs placebo cross-over	100	500µg/100ml	4 months-6 weeks washout-4 months	"firm diagnosis of EPP"	14.71± 6.21	6.81 - 28.6
Mathews 1977	b-carotene only	180-240	>400 µg/L	not indicated, accumulated experience for 7 years	Clinical signs, elevated levels of PPIX in red blood cells and feces	not reported	not reported
Niebauer 1978	b-carotene only	100-200	not determined	1-4 years	not reported	23.4 ± 19.0	5.87 - 51.25
Thomsen 1979	b-carotene only	50-200	> 7µmol/L (>3750µg/L)	between 1 and 5 seasons	not reported	not reported	12-75
Barth 1984	b-carotene only	variable, 60-240 (increase until effective)	>7.45 µmol/L (>4000µg/L)	not mentioned	not reported	not reported	not reported
Wennersten 1980	b-carotene plus canthaxanthin	100	not determined	6 years	porphyrin analysis in blood, urine and feces	not reported	not reported
De Sélys 1988	b-carotene plus canthaxantin	40-75 (betacarotene and 60 -90 canthaxantin)	not determined	one summer	"fluorocytes", elevated PPIX level in red blood cells and feces, decreased ferrochelatase activity	measured as zinc-protoporphyrine; conversion not possible	

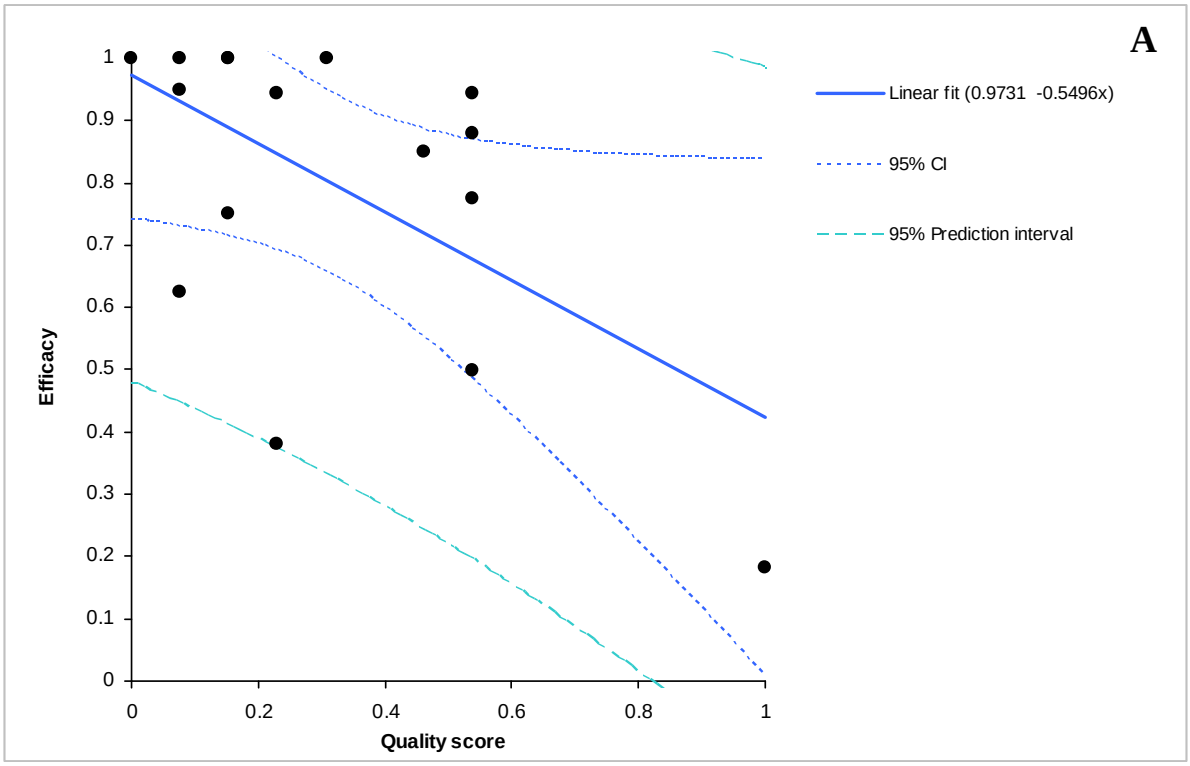
	study design:	Dosage (in mg/d)	minimal b-carotene serum concentration[1)]	duration of study	Patient selection	PPIX in red cells mean ± SD µmol/L	
Lehmann 1991	b-carotene only	individually 75 – 150	not determined	not mentioned	not reported	17.3 ± 9.1	
Laar 1996	different beta-carotene prep.	75-150	1.1 µmol/L(590µg/L)	150 days	all patients suffered from severe EPP	13.31 ± 6.91	4.02 - 45.8

[1)] a factor 537 was used to convert µmol/L into µg/L.

2b: Efficacy of betacarotene studies:

			EPP symptoms			Phototesting			
Study (Author, year)	Study type[1)]	No Pat.	no significant change	moderate effect	strong effect	No of Pat.	unchanged	moderate effect	strong effect
Lewis 1972	case series	4	2	1	1				
Baart 1972	uncontrolled trial	25	3	12	10				
Mathews 1974	uncontrolled trial	53	3	9	41	21	1	16	4
Krook 1974	case series	7	0	0	7				
Beckert 1976	case series	5	0	1	4				
Mathews 1977	uncontrolled trial	80	18	15	47				
Goerz 1977	case series	20	1	10	9				
Zaynoun 1977	case series	16	8	0	8	13	9	3[2)]	1[2)]
Corbett 1977	cross-over controlled	11	9	1	1				
Niebauer 1978	case series	8	3	3	2				
Thomsen 1979	case series	36	2	16	18				
Wennersten 1980	case series	3	0	2	1				
Barth 1984	case series	28	0	7	21				
De Sélys 1988	case series	3	0	3	0				
Lehmann 1991	case series	20	3	6	11				
Laar 1996	case series	18	11	6	1				
Sum		337	62	94	181	34	10	19	5
%		100	18	28	54	100	29	56	15

[1)] Retrospective data collections were categorized as “case series”; prospective data collections without a control regimen as “uncontrolled trials”; and prospective data with random allocation to both active and control as “controlled trials”.
[2)] Change at least of one of several wavelengths tested.



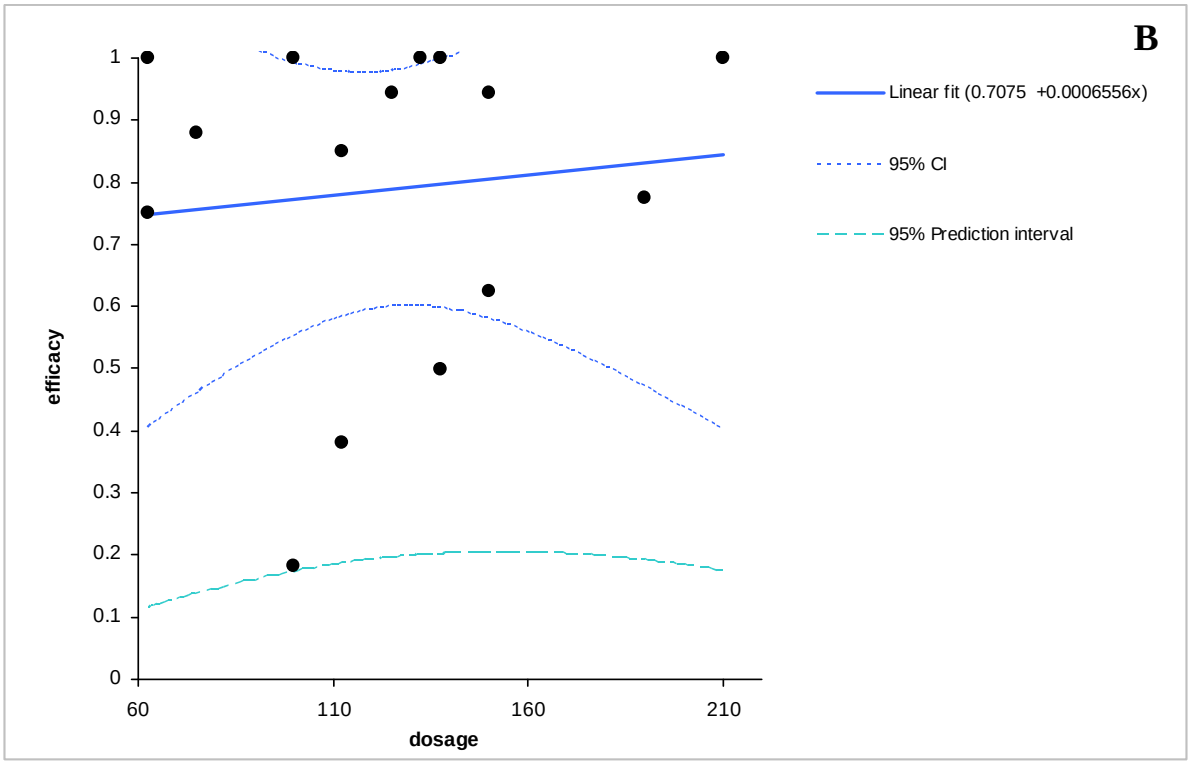


Figure1. The impact of study quality (A) and of dosage in mg/d (B) on efficacy: For study quality, each criterion described in the section "Assessment of Methodological Quality" was scored. The number of fulfilled quality criteria of a trial divided by the total number of criteria was used as quality score. Dosage was expressed as the mean of the ranges given in the publications. The efficacy was expressed as the fraction of patients having moderate or strong improvement of EPP symptoms.

investigators were blinded with respect to treatment. The study showed a high dropout rate i.e., of a total of 51 patients, 4 patients dropped out during the first, 18 during the second and 2 during the third year of study.

NAC a substance closely related to cysteine, was shown to be ineffective in two double blinded studies in which the efficacy assessments were based on phototoxicity symptoms in one study (33), and on patients' reports on sunlight tolerance and phototesting in the other (5). Placebo induced improvement of subjective symptoms was found in 70% of the patients in one study (33) but none in the second study (5).

If the limits of a factor 3 for moderate and 5 for strong effects were applied to those two studies in which numeric data were available (5,29), only one of the 22 patients profited moderately and none of them profited strongly from cysteine and none from NAC.

Miscellaneous agents (Table 4):

Topical DHA/Lawson (henna): Two studies (reported in 3 articles) informed on the application of DHA either alone or combined with Lawson on patients with a variety of photosensitivity diseases including 3 EPP patients in each study (14,15,37). One study reported protective factors between 2.4 and 13.5 in EPP patients. The other study did not group patients according to the underlying disease instead, only stated that 14 sun-sensitive patients experienced a 2 to 5-fold increase, 11 patients a 6-10 fold and 5 patient a more than 11 fold increase in their light tolerance under the therapy. Some inconsistencies are found in this study of 2 years duration e.g., the first sentence in the result section reads "The protection achieved by the patients during each year was similar;…" (37). In a follow-up publication referring to the same study however, a statement reads "During the first year the DHA/Lawson mixture, due to chemical inconsistency, provided minimal and inconsistent protection from sunlight." (15). It was also stated that the left upper extremity served as their own control in one of the 3 groups of patients, but effects between left and right upper extremities were not compared.

Canthaxanthin: Canthaxanthin, a carotinoid like beta-carotene, was applied in an open label trial to porphyria patients, among them 7 suffered from EPP (11). The authors described an improvement in 6 of the 7 patients (moderate improvement in 3 patients and strong improvements in others). Canthaxanthin however, can cause retinal pigmentation and has therefore been withdrawn from the market.

Vitamin C was tested in a double blind, placebo-controlled, randomized and cross-over study (6). The study fulfilled the criteria with respect to patients' allocation, performance and blinding. Eight of the 12 study participants preferred vitamin C, 2 preferred placebo and 2 found no difference between vitamin C and placebo. A non-significant tendency of improvement in sunlight tolerance by vitamin C was concluded by the authors. However, if a 2-tailed statistical limit which is more appropriate than the one-tailed limit is used, the p-value exceeds 0.1.

UVB: Collins and Ferguson (7) applied a narrow-band UVB phototherapy on a number of photosensitive patients including 6 EPP patients. They determined minimal erythemal doses at different wavelengths and daily tolerance of direct sunlight, both showing an increase after the treatment. A sunlight tolerance of maximal 2 h was achieved in EPP patients. This clinically open study had however neither a control group nor a control of seasonal effects.

DISCUSSION

Efficacy determination in EPP

The severity of EPP related skin symptoms is often understated in textbooks as itching, tingling or burning. In fact, a painful sensation in the skin develops immediately or within a few minutes of sun irradiation. After a prolonged exposure, the pain due to a phototoxic reaction becomes intolerable which can last for several days. The phototoxic skin reaction in EPP is often accompanied by an increased sensitivity to touch, heat and cold, and may progress to edema, purpura, wheals or lesions (40,41,42). Some patients describe additional constitutional symptoms such as fatigue and prostration for a prolonged period of time. Some patients, after reaching adulthood, manage to avoid phototoxic reactions; however others suffer from several attacks every year during the sunny and hot seasons. Despite the dramatic suffering of EPP patients, efficacy measurement is difficult and has not been standardized.

Potential therapeutic endpoints are "tolerated time of sunlight exposure" and "number and intensity of phototoxic reactions".

Table 3. Cysteine and N-Acetyl-cysteine studies

Study (Author, Year)	study design[1)]	dosage mg/d	study duration	Patient selection	PPIX in red cells		No Pat.	EPP-Symptoms			Allocation	Performance	Attrition bias	Detection bias
					mean ± SD µmol/L	range µmol/L		no significant change	moderate effect	strong effect				
Bijlmer-Iest 1993	double blind, placebo controlled, cross-over	NAC: 1800	3 weeks treated 3 weeks wash-out 3 weeks treated	typical symptoms, raised EC-PPIX	37.12±9.69	25.2-49.0	6	6	0	0	randomized, cross-over	double-blind	all patients completed the study	no precautions reported
Mathews 1994	double-blind, cross-over, placebo controlled	CYS 1000	8 weeks treated 1 week washout 8 weeks treated	not reported	not reported	not reported	16	15	1	0	randomized, crossover	double-blind	1 patient dropped out last visit	no precautions reported
Norris 1995	double blind, placebo controlled, cross-over	NAC: 600	4 weeks treated 1 week washout 4 weeks treated	not reported	not reported	not reported	15	NAC: 2 Placebo: 3	NAC: 8 Placebo: 6	NAC: 5 Placebo: 5	randomized, cross-over	double-blind	1 patient dropped out	no precautions reported
Mathews 2002	single blind	CYS 1000	1 month placebo, then active drug	not reported	not reported	not reported	51 (47/29/22)	25 patients reported significant increase in time to symptom development...on bright days ...between 8am and 4pm....p<0.001 CYS vs placebo			no rando-mization	single-blinded (Patients only)	4 p. first year, 22 p. second year, 24 p. 3rd year	no precautions reported

[1)] Retrospective data collections were categorized as “case series”; prospective data collections without a control regimen as “uncontrolled trials”; and prospective data with random allocation to both active and control as “controlled trials”.

Table 4. Miscellaneous agents

Study (Author, year)	study design[1)]	test-substance	duration of study	Patient selection	PPIX in red cells		No Pat.	EPP-symptoms		
					mean ± SD µmol/L	range µmol/L		no change	moderate effect	strong effect
Fusaro 1975	open label (pretreatment-posttreatment comparison)	DHA/lawson	Several weeks	5 pat. with photocuta-neous symptoms	not reported	not reported	3	1[(2)]	0	2
Rice 1976	uncontrolled trial (left arm as control in 7 probands)	DHA/lawson	7-8 months	a group of patients with a variety of clinical photosensitivity	not reported	not reported	30 photo-sensitive patients (3 EPP)[(3)]	2	10	18
Eales 1978	uncontrolled trial	canthaxanthin	variable, 7-16 months	not reported	15.76±11.34	1.8-31	5 (+ 2 with VP and 2 with SP)	1	3	3
Collins 1995	case series	UVB	6-7 months (March/April to October)	history, physical examination, red blood cell fluorescence	not reported	not reported	6	1	1	4
Boffa 1996	double-blind, placebo-controlled, crossover	Vitamin C	4 weeks - 4 weeks crossover	"known to suffer from EPP"	If units are converted to µmol/L EC the resulting values are incredible (Ref value < 33 µmol/L, the median at 240 and the range from 125 - 460 µmol/L)		12	better during active 8 no change 2 better during placebo 2		

1) Retrospective data collections were categorized as “case series”; prospective data collections without a control regimen as “uncontrolled trials”; and prospective data with random allocation to both active and control as “controlled trials”.
2) VAS sunlight tolerance: 0 no change, +5 maximal improvement, -5 maximal deterioration; unclear data, as each patient should exhibit zero at study begin, which is not the case.
3) Results only summarized for all different photosensitive diseases.

As patients (at least adults) tend to adjust their tolerance, these two variables interact with each other. Thus, efficacy may be inter-individually variable either as a change in sunlight tolerance, in phototoxicity or in both.

All but one study used some form of "(sun-) light tolerance", however, the method of determination varied. Interestingly, the intensity of spontaneous phototoxic symptoms was used only in two studies (8,33). However, a combined evaluation of phototoxic symptoms and sunlight tolerance was not applied in any of the studies. Such a combination likely would result in improved sensitivity of efficacy assessment because of individual adaptations to the disease. Appropriately designed diaries to record daily outdoor activities deliver higher reliability and less biased information than any retrospective exploration. The term "outdoor activities" needs a careful definition to include all activities that may provoke symptoms. Daily measurements of phototoxic symptoms by VAS can be easily included in such a diary.

Symptom provocation by either artificial or natural light was claimed to be an "objective assessment" (29). As examiners subjectively determine the results of phototesting, they may be biased by their a priori knowledge or their observations in either open-label studies or in studies in which the active compound induces visible changes of the skin color. Nonetheless, photoprovocation may be useful in early study phases of a new therapeutic principle because of its independence of the variations in natural light intensities. Finally, conclusiveness of any efficacy determination is only clarified if (1) an effective treatment is available and (2) a randomized and blinded trial is performed.

Interpretation and conclusion on results of analyzed studies:

Not surprisingly, our search revealed that the majority of the studies (16/25) involving a majority of the overall number of patients (337/454), dealt with the application of beta-carotene. All but one of these beta-carotene studies being open-labeled and uncontrolled are encumbered with a considerable risk of overestimating the positive effects (20). The existence of such an effect is supported by the inverse correlation between study quality and efficacy. The long-term clinical experience of porphyria experts and studies on patient's compliance may take part in decision making. One expert in this field Dr. T. Cox stated "It must be admitted, however, that many patients are disappointed with the effects of β-carotene..."(9). Moreover, only about one third of the patients were long-term compliant to beta-carotene treatment in an large British EPP cohort (18). Despite the conception that an increase in betacarotene dose improves response rate (23), our data revealed no correlation between dose and efficacy. In conclusion, our data compilation let us to the assumption that only a minority of all patients profited from beta-carotene. Since beta-carotene, used at a much lower dose than that in EPP, was suggested to increase the risk of pulmonary malignancy in smokers in some but not all studies (1,17,34), we recommend a careful risk/benefit assessment before long-term beta-carotene therapy is instituted in EPP.

Three of the four more recent studies on efficacy of cysteine and N-acetyl-cysteine fulfilled the current quality requirements although the results of these studies revealed certain unexplainable discrepancies between these two closed related compounds. Cysteine with an apparently good efficacy, has never been marketed as a drug, but is available as a nutritional additive. Because of the high drop out rate during the long-term studies, we assume that a minority of the patients had profited from this substance.

In the last group of agents, DHA/Lawson will not only give the patients a cosmetically unacceptable appearance, but also will raise serious concern over its potential carcinogenic feature, especially when it is used in long-term therapeutic applications such as EPP. We assume that these might be some of the reasons why DHA/Lawson have so far not yet been marketed as skin cream. Based on the available data, vitamin C cannot be recommended to treat EPP. UVB treatment looks promising. However, the lack of reliable data and the significant adverse effects such as grade II erythema, hinder its practicability as a mean of treating EPP.

In conclusion, no undisputed and significant efficacy was shown in any of the therapeutic modalities applied in EPP so far. Given the sufferings which the patients have to endure, there is a need for new and improved options in EPP treatment.

ACKNOWLEDGEMENT

EIM is supported by the Velux-Foundation (Nr 480) and by the Hartmann-Müller Foundation (Nr. 1187). We thank for the support by Ms Karin Meier, librarian of Triemli Hospital.

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