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CLINICAL REPORT

Porphyria Cutanea Tarda: Effects and Risk Factors for Hepatotoxicity from High-dose Chloroquine Treatment

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High-dose chloroquine therapy for porphyria cutanea tarda is rarely used now because of its hepatic side-effects. The mechanisms of the effects and side-effects are poorly understood. We describe here effects, side-effects and long-term follow-up in 57 patients with a first-time diagnosis of porphyria cutanea tarda treated with 1–3 phlebotomies followed by 250 mg chloroquine phosphate daily for 7 days. A hepatotoxic reaction with high serum aminotransferases occurred in almost all patients. Within 3 months, clinical remission was obtained in all patients, and biochemical remission in almost all patients. Relapse occurred in 27 patients after 0.5–12 years. Subjective side-effects occurred more frequently in women, who also had higher maximum ALAT, ferritin and roporphyrin values during treatment. Both subjective side-effects and ALAT during treatment correlated with pre-treatment uroporphyrin excretion and maximum uroporphyrin during treatment, but not with markers of hereditary haemochromatosis. *Key words: porphyria cutanea tarda; chloroquine; phlebotomy; hepatitis C; haemochromatosis.*

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Porphyria cutanea tarda (PCT), the most common type of porphyria, results from reduced activity of the enzyme uroporphyrinogen decarboxylase (UROD) (1). Three different main therapeutic modalities are currently used: repeated phlebotomies; low-dose chloroquine; or a combination of both (2–7). High-dose chloroquine has not been widely used in spite of positive reports about its effect (8–11). Reluctance to use this form of treatment may be related to the well-known hepatotoxic effects of chloroquine in patients with PCT. We report here the results of our study to find possible predictors of hepatotoxicity and side-effects associated with high-dose chloroquine treatment in 57 patients with PCT. Since published treatment studies have had relatively short follow-up periods we also wanted to report the long-term results of this treatment modality.

MATERIALS AND METHODS

Patients

This is a retrospective study of 57 patients (36 men and 21 women) with a first-time diagnosis of PCT, treated during the period 1978 to 1997 and followed-up until 2005. Fifty-three of these patients were followed up for 0.5–25 years (median 11 years). One patient died from a renal carcinoma after 6 months, 3 did not attend check-ups. All patients have been reported in a previous paper and all were followed up by one of the authors (IRR) (12). The diagnosis was based on characteristic clinical features, together with a typical urinary porphyrin pattern of marked increases in uro- and heptacarboxy-porphyrins. Risk factors for clinical manifestation of PCT are given in Table I.

The mean time between first cutaneous symptoms and diagnosis was one year. The median age for clinical manifestation of PCT was 61 years for women and 59 years for men. The hereditary pattern for the disease and the patients' alcohol habits were analysed by questioning the patients. Alcohol abuse was diagnosed when the patient admitted to daily or almost daily consumption. A hereditary pattern for the disease was reported by 9 women and 7 men. Analysis for mutations of the haemochromatosis gene (HFE) C282Y and H63D was performed in 34/57 patients who were still under follow-up when this testing was introduced in 1997. Hepatitis C virus (HCV) tests were introduced in 1992, thus 15 patients who were lost for follow-up at that time were never tested. Fourteen out of 31 tested patients who did not have overt diabetes mellitus had a positive oral glucose tolerance test.

Urinary and faecal porphyrins were analysed by thin layer chromatography and spectrofluorometry. Porphyrins in urine were concentrated by absorption to calcium phosphate before elution with HCl and determination by spectrophotometry. Porphyrins were concentrated and converted to their methyl ester

Table I. *Risk factors for clinical manifestation of porphyria cutanea tarda (PCT) at the time of diagnosis*[a]

	Women *n* (%) 21 (37)	Men *n* (%) 36 (63)
Age at onset (years) Median (range)	61 (34–81)	59 (29–77)
Heredity for PCT	9 (43)	7 (19)
HFE CYS/CYS	3/15 (20)	1/19 (5)
HFE CYS/HIS	4/15 (27)	1/19 (5)
Anti-HCV-positivity	0/18 (0)	7/24 (29)
Diabetes mellitus	4 (19)	7 (19)
Oestrogen	9 (43)	0 (0)
Alcohol abuse	1 (5)	12 (33)
No identified risk factor	4 (19)	9 (25)

[a]Some patients have more than one risk factor.
HFE: haemochromatosis gene; CYS: CYS282Tyr; HIS: His63Asp; HCV: hepatitis C virus.

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derivatives before separation by thin layer chromatography. Faecal porphyrins were extracted with ether from an acidified sample. Coproporphyrin was extracted from the ether with HCl 0.1 mol/l, protoporphyrin with HCl 1 mol/l. The concentration was determined by spectrophotometry.

Treatments

After 2–3 phlebotomies of altogether in average 750 ml of blood, chloroquine phosphate, 250 mg daily, was given orally for 7 days. This treatment modality has been described previously (8, 10). Before the phlebotomies, pre-treatment laboratory evaluation was performed. The ethics committee of the hospital approved the high-dose chloroquine modality. The patients were hospitalized during the chloroquine treatment, enabling closer laboratory follow-up. Thus, liver enzymes and urinary porphyrins were measured daily during the high-dose chloroquine treatment period.

Treatment modalities after relapse and times to relapse are illustrated in Fig. 1. In the following text all laboratory data refer only to the first treatment episode in each patient.

Phlebotomy as monotherapy was used:

- as the primary and recurrence treatment modality in all patients after 1997. The potential of serious side-effects and the necessity of clinical intensive observation during treatment were the reasons why, after 1997, all recurrences were treated with phlebotomy.
- before 1997, as treatment of recurrence in chloroquine-treated patients who had serious side-effects from the previous chloroquine treatment.

Phlebotomy was performed by withdrawal of 400 ml blood weekly. Phlebotomy was stopped when the patient's serum iron level fell below the lower limit of normal (LLN) (9 μmol/l), the transferrin saturation was below LLN (15%) and/or the ferritin was below LLN (15 μg/l for men and 10 μg/l for women). Repeated phlebotomies were performed 3–6 times annually in patients with genetic haemochromatosis and in compound positive patients who had signs of iron overload. Oestrogen therapy was discontinued in the nine women who were on this form of treatment.

Urinary and faecal porphyrin excretion, serum liver enzymes, haemoglobin, transferrin saturation, and ferritin were scheduled to be measured before the pre-treatment phlebotomies, during the treatment and 3 months later. If the laboratory values were normal after 3 months, the patients were only controlled as outpatients once yearly. If the patient demonstrated urinary porphyrin above the upper limit of normal (ULN), a new check-up was performed 3 months later. If this check-up demonstrated an increase in urinary porphyrins up to at least 3×ULN, this was considered a recurrence.

Statistics

Correlations between continuous variables were tested using a Spearman's correlation test, and between numerical data using a contingency test. Differences between continuous data were tested using a Mann-Whitney *U* test. The level of significance was 5%.

RESULTS

Before treatment

ASAT (serum aspartate amino transferase activity) and ALAT (alanine aminotransferases) were increased before treatment in 32 and 48 of the 57 patients, respectively. As is evident from Table II, increased levels before treatment were also seen in uropophyrin and in most patients also in ferritin and transferrin saturation.

Early effects of chloroquine treatment

As is evident from Table II, the treatment was followed by a marked increase in serum ALAT, ferritin and urinary porphyrins. Maximum ALAT values during treatment were higher in females (p=0.0001) than in males, and correlated with maximum serum ferritin (p <0.0001) and urinary porphyrins (p <0.0001) during treatment, and with pre-treatment urinary porphyrins (p=0.0023), but not with the presence of haemochromatosis gene (HFE) gene mutations, anti- HCV-positivity or with pre-treatment serum ferritin or transferrin saturation. The maximum serum ferritin during treatment correlated with pre-treatment ferritin (p=0.0266), but not with the presence of HFE gene mutations. Female patients had higher serum ferritin (p=0.0039) and uroporphyrins (p=0.0005) during treatment than male patients.

Twenty-five out of 57 patients treated with chloroquine phosphate experienced influenza-like symptoms (fever and/or nausea). Treatment was stopped prematu-

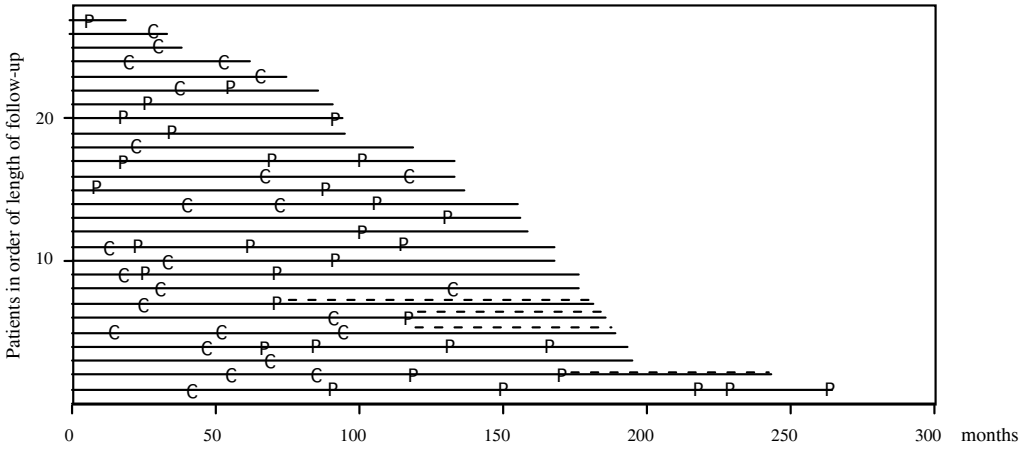

Fig. 1. Total follow-up and time to recurrence and new treatments with chloroquine (C; one week) or phlebotomy monotherapy (P) in 27 patients treated primarily with chloroquine. Dotted lines indicate repeated phlebotomies. The time between the letters represents the time of remission.

Table II. *Laboratory values before, during (maximal) and after treatment with high-dose chloroquine*

	Before			Maximal			After 3 months		
Analysis	Total	Men	Women	Total	Men	Women	Total	Men	Women
Uroporphyrin (mmol/mol creatinine×ULN)									
Median	10.5	9.75	12.0	47.5	32.5	115	0.5	1.45	0
Range	2.25–37.5	2.25–30.0	3.5–37.5	6.5–300	6.5–145	15–300	0–9.5	0–9.5	0–3.5
Uroporphyrin (mmol/period×ULN)									
Median	6.83	6.75	7.0	38.3	24.17	88.33	0	0.74	0
Range	2–26.7	2.0–26. 7	2.0–25	5–217	5.0–113	7.16–217	0–7.1	0–7.17	0–1.6
ASAT×ULN									
Median	1.08	0.95	1.38	5.0	3.25	18.33	0.72	0.7	0.78
Range	0.42–6	0.42–3	0.5–6	0.82–75	0.82–17.5	1.66–75	0.31–1.62	0.37–1.62	0.31–1.46
ALAT×ULN									
Median	1.62	1.5	1.88	7.0	4.5	21.67	0.88	0.88	0.82
Range	0.48–8.0	0.48–5.9	0.8–8.0	1.1–55	1.1–27.5	2.0–55	0.18–3.38	0.39–3.38	0.18–1.53
Ferritin×ULN									
Median	1.29	1.17	1.36	5.8	3.04	12.14	0.85	0.85	0.93
Range	0.14–12.6	0.23–8.17	0.14–12.6	0.2–75.4	0.59–65.2	0.2–75.4	0.07–7.79	0.2–2.97	0.07–7.79
Transferrin saturation (%)									
Median	43	44.5	43	ND	ND	ND	ND	ND	ND
Range	18–98	18–98	28–85						

×ULN: times upper limit of normal; ASAT: serum aspartate amino transferase activity; ALAT: serum alanine amino transferase activity; ND: not

rely after 2–4 days in 4 patients because of influenza-like symptoms with very high serum amino transferases.

The occurrence of influenza-like symptoms correlated significantly with maximum ALAT (p <0.0001) and ferritin (p=0.0008) and with maximum urinary porphyrins (p <0.0001). It was also significantly associated with female gender (66 vs. 28%, p=0.0058) and pre-treatment urinary porphyrins (p=0.048), but not with age, HFE gene mutations positivity or anti-HCV positivity or with pre-treatment ALAT, serum ferritin or transferrin saturation.

There was no significant difference in incidence of side-effects related to whether the patient had the hereditary or spontaneous form of PCT, nor were there any significant differences related to the other identified risk factors.

Follow-up

Complete disappearance of skin manifestations was observed in all patients. Before treatment the median value for uroporphyrin in 24 h urine was 6.8×ULN (range 2.25–32.5×ULN). Twenty-nine patients had no measurable uroporphyrin excretion within 3 months after treatment. Eighteen patients had a porphyrin excretion 1–2×ULN within 3 months and subsequently their uroporphyrin excretion normalized. Four other patients, who did not attend earlier follow-ups, had a normalized uroporphyrin excretion within 12 months. Two patients who did not have normalized porphyrin excretion after one year were subsequently treated anew. Four patients were lost to follow-up. Nine of the 53 patients with a follow-up of at least 7 months had persistently elevated, albeit lower than pre-treatment, levels of ALAT (1.3–3.3×ULN). Seven of them had one or several possible explanations for this abnormality, e.g. metabolic syndrome, chronic hepatitis C or alcohol abuse.

As mentioned previously, patients identified as having haemochromatosis or compound positive for the HFE mutations and who had biochemical evidence of iron overload were treated with repeated phlebotomies 3–6 times a year. Recurrences were not observed in any of these patients.

Twenty-seven patients experienced biochemical recurrence after 7–144 months (mean 44, median 36 months). The follow-up periods for the patients with recurrence are illustrated in Fig. 1. Thirteen patients had a recurrence within 3 years: recurrence after treatment or the time to recurrence was not significantly related to whether or not the patient had experienced side-effects, nor was it related to gender, ALAT maximum, ferritin maximum or porphyrin maximum during treatment. However, 6 were anti-HCV positive, 2 were subsequently shown to be positive for HFE gene mutations, 2 had a positive desferoxamine test, 2 were alcohol abusers, and one re-instituted oestrogen. As is evident from Fig. 1, many patients received iterated treatments with chloroquine, in a single case as many as 4 treatment episodes. The median time to recurrence after the first and second chloroquine treatment for recurrence was 39 (range 17–100) months and 35 (30–40) months, respectively. The median time to recurrence after the phlebotomy treatments was 40 (range 18–82) months.

DISCUSSION

In conformity with previous reports the present study demonstrated a high incidence of side-effects in the

form of influenza-like symptoms and also of increased serum amino transferase levels (13). Chloroquine is not a known hepatotoxin. Even in overdose it does not cause significant liver damage (14). Animal experiments aimed at elucidating the mechanism of the liver injury associated with high-dose chloroquine treatment have given contradictory results (15–17). Furthermore, there is, to our knowledge, no histopathological study in which liver biopsies have been performed in close association with high-dose chloroquine treatment of PCT. Thus, the mechanism of the liver injury remains speculative.

An increased risk of side-effects in HFE gene mutation positive patients has been reported previously in association with low-dose chloroquine treatment (18). In the present investigation, we found no relationship between HFE gene mutations or pre-treatment serum ferritin or transferrin saturation levels and the occurrence of side-effects or maximum ALAT increase. Admittedly, the number of such patients was small. In the total material, there was a significant correlation between maximum serum ferritin levels during treatment and both subjective side-effects and maximum serum ALAT increase. However, high serum ferritin levels, a marker of inflammatory reactions, are seen also in other types of liver disease (19, 20), and these correlate with serum ASAT levels, but not with hepatic iron content in chronic viral hepatitis (19). Thus, the high serum ferritin levels are probably only a marker of liver cell damage.

In contrast to the lack of correlation between the occurrence of side-effects or ALAT increase during treatment, and markers of iron overload besides serum ferritin, there was a strong correlation between both subjective side-effects and maximum ALAT increase on the one hand, and pre-treatment and maximum urinary porphyrin levels on the other hand. Both subjective side-effects and grade of hepatotoxicity thus seem to be primarily related to the degree of porphyrin overload and the porphyrin emptying effect of the treatment.

We observed a higher sensitivity to liver injury, evident from the higher rate of symptoms, higher ALAT and the higher serum ferritin during treatment, in females compared with males. It is evident, that the more pronounced liver injury is related to a higher release of uroporphyrins from the liver in females. A tentative explanation for this gender difference could be that the female patients have received a higher dose of chloroquine in relation to body weight, than the male patients. However, there was no relationship between the body weight and the maximum ALAT or ferritin levels during treatment. The reason for the gender difference therefore remains elusive.

To conclude, high-dose chloroquine treatment for PCT is associated with a high rate of influenza-like symptoms and often a pronounced increase in serum amino transferases. Both these side-effects are related to the amount of porphyrin excreted during treatment and to pre-treatment urinary porphyrin levels, but not to other identified risk factors for clinically overt PCT, e.g. hereditary haemochromatosis. Almost half of the patients had no recurrence during long-term follow-up. Half of the recurrences occurred within 3 years after treatment. Similar results have been reported after phlebotomy treatment (2, 7). All patients having recurrence after chloroquine treatment had at least one known risk factor for overt PCT disease.

To our knowledge, high-dose chloroquine treatment is no longer used in the treatment of PCT in Sweden. Low-dose chloroquine treatment in combination with phlebotomy treatment is used at some hospitals, in patients with or without HFE gene mutations.

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