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RESEARCH REPORT

Audit of the Use of Regular Haem Arginate Infusions in Patients with Acute Porphyria to Prevent Recurrent Symptoms

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Abstract The National Acute Porphyria Service (NAPS) provides acute care support and clinical advice for patients in England with active acute porphyria requiring haem arginate treatment and patients with recurrent acute attacks.

This audit examined the benefits and complications of regular haem arginate treatment started with prophylactic intent to reduce the frequency of recurrent acute attacks in a group of patients managed through NAPS. We included 22 patients (21 female and 1 male) and returned information on diagnosis, indications for prophylactic infusions, frequency and dose, analgesia, activity and employment and complications including thromboembolic disease and iron overload.

The median age at presentation with porphyria was 21 years (range 9–44), with acute abdominal pain as the predominant symptom. Patients had a median of 12 (1–400) attacks before starting prophylaxis and had received a median of 52 (0–1,350) doses of haem arginate. The median age at starting prophylaxis was 28 years (13–58) with a median delay of 4 years (0.5–37) between presentation and prophylaxis. The frequency of prophylactic haem arginate varied from 1 to 8 per month, and 67% patients were documented as having a reduction in pain frequency on prophylaxis. Only one patient developed clinically significant iron overload and required iron chelation, but the number of venous access devices required varied from 1 to 15, with each device lasting a median of 1.2 years before requiring replacement. Six patients stopped haem arginate and in three this was because their symptoms had improved. Prophylactic haem arginate appears to be beneficial in patients with recurrent acute porphyria symptoms, but maintaining central venous access may prove challenging.

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Introduction

The porphyrias are rare metabolic disorders caused by defects in the synthesis of haem and are usually associated with either acute or cutaneous symptoms or a mixture of both. The three main types of acute porphyria are acute intermittent porphyria (AIP), variegate porphyria (VP) and

hereditary coproporphyria (HCP). Acute porphyrias cause sudden-onset, unpredictable episodes of illness, characterised by severe abdominal pain, gastrointestinal symptoms, hypertension, hyponatraemia and varying degrees of additional neurological impairment (Puy et al. 2010). Typically the diseases are inherited as an autosomal dominant trait, although many people with acute porphyria have few or no symptoms with penetrance within affected families being reported as between 10 and 50%. AIP is the most common of the acute porphyrias and, unlike VP and HCP, is not associated with bullous skin lesions. Most symptomatic patients have only one attack, but approximately 5% women and 3% men with porphyria suffer recurrent and frequent attacks which persist for many years (Elder et al. 2013).

An acute porphyria attack can be life threatening, and severe episodes usually require hospital admission and treatment with a preparation of intravenous solubilised haem, by supplying the end product of the biosynthetic pathway. Haem therapy decreases the formation of porphyrin precursors, overproduction of which is believed to be responsible for the acute clinical compensation. In Europe, haem therapy is available in the form of haem arginate (Normosang®). Patients may also require high doses of opiate medication to relieve the pain suffered during the attack (Stein et al. 2013).

Recurrent severe attacks are rare and affect about 5% of patients with acute porphyria; typically recurrent attacks occur in women in association with the menstrual cycle and usually improve after the menopause. Severe attacks may occur more frequently than monthly and can be associated with progressive neuropathy, chronic pain, renal impairment and increased risk of hepatocellular carcinoma (Sardh et al. 2013). Frequent attacks result in severe disability, making normal working, family and social life very difficult. It is thought that 20–30 individuals in the UK currently suffer from this pattern of frequent recurrent attacks.

There is little evidence published on how to manage these patients optimally; the therapeutic options include suppression of menstruation with gonadorelin (GnRH) analogues (Anderson et al. 1990), regular haem arginate infusions (Stein and Cox 2011) and, in a few cases, liver transplantation (Soonawalla et al. 2004; Dowman et al. 2011).

There is some evidence that haem arginate infusions are of benefit in shortening the duration and severity of single acute attacks of porphyria, with a rapid fall in urinary concentrations of porphobilinogen (PBG) and other metabolites indicative of an acute attack (Herrick et al. 1989; Ma et al. 2011). Based on this acute effect and licenced use, regular haem arginate infusions have been used in an attempt to prevent recurrent attacks for at least 20 years. As many as six infusions have been given each month usually via an indwelling central line. Anecdotally some patients benefit from this, although published data are lacking. Conversely, significant side effects can occur, including central venous thrombosis and iron overload, and chronic pain may persist.

The aim of this audit was to evaluate the benefits and complications of haem arginate prophylaxis in patients with recurrent acute attacks of porphyria and where possible to develop preliminary evidence-based guidelines for its use.

Design and Methods

Patients were identified from the records of the three acute porphyria centres in England and Wales. Any patient with a diagnosis of acute porphyria who had started haem arginate infusions with prophylactic intent from 1999 to 2012 was included.

All patients in England who started regular prophylactic haem arginate were identified from records of the National Acute Porphyria (NAPS) centres in Cambridge, Cardiff and London and outreach clinics in Leeds and Salford and from the records of Orphan Europe, who are exclusive suppliers of haem arginate in the UK. Audit data was collected using an agreed proforma (Table 1) through a combination of examining patient records both at NAPS centres and local hospitals. Qualitative data on activity levels and employment before, during and after prophylaxis was also collected.

Results

Patients

Twenty-three patients (21 females, 2 males) (Cardiff/Salford, 7 patients; Cambridge/Leeds, 12 patients; and King's College Hospital, 4 patients) had received prophylactic haem arginate treatment. One patient had variegate porphyria (VP), one hereditary coproporphyria (HCP), twenty acute intermittent porphyria (AIP) and one post-liver transplant (who was not included in subsequent analyses). All diagnoses were confirmed by biochemical analysis, with increased urine porphobilinogen (PBG) measurements at the time of presentation; the differential diagnosis of VP, HCP or AIP was established by biochemical porphyrin investigations and genetic analysis.

Presenting Features

The median age of symptomatic presentation and diagnosis of acute porphyria was 21 years (range 9–44 years). Most

Table 1 Parameters studied during the audit

	Parameters studied
Diagnosis and history before prophylaxis	Type of porphyria and biochemical diagnosis
	Date, place of diagnosis and presenting symptoms
	Age of first acute symptoms and precipitants
	Number of hospital admissions, haem arginate doses and regular analgesia
	Treatment with GnRH agonist: type, duration, reason for stopping
	Iron indices: ferritin, serum iron and transferrin saturation
	Other relevant co-morbidities
	Quality of life (QOL): employment, activity, exercise
Prophylactic haem arginate	Frequency and dose of haem arginate and route of administration
	Duration of treatment including reason for stopping treatment
	Frequency of acute and chronic symptoms
	Number of hospital admissions, haem arginate doses and regular analgesia
	Iron indices: ferritin, serum iron and transferrin saturation
	Other relevant co-morbidities
	QOL: employment, activity, exercise
After prophylactic haem arginate	Treatment with GnRH agonist: type, duration, reason for stopping
	Iron indices: ferritin, serum iron and transferrin saturation
	Regular analgesia
	QOL: employment, activity, exercise

presented with an acute attack, with abdominal pain as the dominant feature. Three patients were asymptomatic when diagnosed as part of family screening but subsequently developed acute symptoms. The presenting features of porphyria in patients with recurrent attacks do not differ obviously from the initial symptoms of porphyria patients in general, including those who have only had a single attack.

History Before Prophylaxis

The number of acute attacks requiring hospital admission before prophylactic treatment varied, with a median of 12 (range 1–400). One patient started prophylactic haem arginate after a single admission lasting 7 months. The number of days in hospital was also very high with a median 94 days (range 20–2,000). Patients received a median of 52 doses (range 0–1,350) of haem arginate before being started on prophylaxis, given as treatment for acute attacks.

GnRH agonists were prescribed for 15/21 (71%) of the female patients before starting prophylaxis with haem arginate. Three patients were also given oestrogen replacement during treatment, and the median time of treatment was 6 months (1 month to 3 years). Eleven patients stopped GnRH agonists because the treatment was ineffective and acute attacks persisted; one patient continued on GnRH agonists with regular haem arginate. The other reasons for stopping treatment are shown in Table 2.

Prophylactic Haem Arginate Treatment

The median age of starting prophylactic haem arginate treatment was 28 years (range 13–58), and the median time between onset of symptoms and starting prophylaxis was 4 years (0.5–37 years). No standard treatment regimen was used, and the dose was 3 mg/kg for each patient referred to as "dose" in the text. Approaches differed for each patient and varied depending on physician choice, the frequency of acute attacks and linkage to the menstrual cycle. Four patients were prescribed one dose of haem arginate monthly, three patients twice per month, thirteen patients four times per month, one patient six times per month and one patient eight times per month. Fifty percent of the patients were also on regular opiate analgesia because of chronic pain. The duration of prophylaxis varied with a median of 50 months (range 1–150) and a median of 150 (2–1,000) doses of haem arginate used; 16 patients continued on haem prophylaxis beyond the end of the audit period, into January 2013. Table 3 shows the dose

Table 2 Reasons for stopping GnRH treatment

Agonist	Length of treatment	Oestrogen	Reason for stopping treatment
Leuprorelin	4 months	No	TAH and BSO
Not known	3 months	Patch	No benefit
Goserelin	1 month	No	Exacerbated an acute attack
Goserelin	<12 months	Tibolone	Ineffective
Goserelin	8 months	No	Side effects, attacks continued
Not known	Not known	No	Ineffective
Goserelin	6 months	No	Acute attacks continued
Buserelin then Goserelin	Not known	No	Not known
Goserelin	3 years	No	Monthly attacks continued
Goserelin	6 months	No	Attacks stopped then relapsed
Not known	9 months	No	Precipitated several acute attacks
Goserelin	6 months	No	Attacks persisted
Goserelin	4 months	No	Ineffective
Goserelin	7 months	Tibolone	Acute attacks continued
Goserelin	<12 months	No	Ineffective. Attacks persisted

schedule and cumulative doses given to each patient over the treatment period.

While receiving these prophylactic measures, eight (36%) patients had no hospital admissions, eleven (50%) were admitted between 1 and 5 times/year, and three (14%) were admitted more than 5 times per year. The median number of admissions was 9 (range 0–100). Fourteen (67%) patients showed a decrease in pain frequency on haem prophylaxis compared with before it had been started; six (29%) reported no change; one (5%) had an increased frequency of symptoms; and it was too early to evaluate one patient.

The activity and exercise capacity were assessed qualitatively; the activity level of one (5%) patient was worse following prophylactic haem treatment, while 8 (40%) patients showed no change and 11 (40%) noted an improvement. Seven (35%) patients showed improved work capacity on haem prophylaxis, 12 (60%) showed no change, and 1 (5%) showed reduced capacity.

One of the potential effects of haem treatment is iron overload. Each ampoule of haem arginate (10 mL, 250 mg of human haemin) contains 22 mg of iron. Serum ferritin concentrations were available in 19 patients and showed a median of 208 μg/L (reference range: 20–200), but there was a wide range (21–3,165 μg/L). Transferrin saturations were available in 16 patients, with a median of 29% (reference range: 20–50%) and a range of 9–100%. One patient was receiving iron chelation, but as far as could be ascertained, no patients had organ damage related to iron overload. There was a statistically significant correlation between serum ferritin concentration and the number of doses administered ($r = 0.884$, $p < 0.001$), and the data is shown in Fig. 1. Ferritin concentrations were proportionately more elevated than transferrin saturation, with 53% (10/19 patients) having serum ferritin determinations greater than the upper reference limit, compared with only 23% with raised transferrin saturations; two patients had transferrin saturations below the normal reference range.

The number of semi-permanent central venous access devices used during prophylactic haem treatment and the reasons for removal of a device were available from 20 patients. The number of devices used per patient ranged from 1 to 15. The median number of devices used per patient was two, and eight patients had only one device fitted. There were a total of 52 devices removed, and the average lifespan for a single device was 1.2 years. There was a correlation between the number of devices used and cumulative dose received, but this was not statistically significant possibly as a result of the limited number of patients in the study (Fig. 2). The reasons for removal of the devices were infection (8%), blockage (35%) and a mixture of infection/blockage (38%) and single cases of thrombosis, infection/thrombosis, difficulties with venous access and pain.

Table 3 Dosage schedule and cumulative doses of haem arginate with complications

Patient	Dosage schedule	Total monthly dose (3 mg/kg/dose)	Total doses	Treatment period (months)	Number of devices used	Complications	Ferritin ug/L (normal: 20–300)
1	MX2	2	8	4	1	None	21
2	M	1	40	40	1	None	50
3	MX4, MX2, M	4	73	30	3	Location	Unknown
4	MX4	4	250	62	10	Three infected, one blocked	Unknown
5	MX3, MX2, MX4	4	58	29	1	Blocked but okay	140
6	MX4	4	30	7	1	None	84
7	MX2	2	100	50	1	None	208
8	M	1	144	144	Unknown	None	37
9	MX4	4	2	1	1	None	89.2
10	MX2, M	1	200	132	1	Unknown	44.9
11	M, MX2, MX4	4	450	132	5	Infection/ thrombosis	258.2
12	MX2	2	50	25	4	Infection/ thrombosis	45.9
13	MX4, MX8, MX4	4	275	69	Unknown	Unknown	701
14	MX6	6	1,000	150	15	Infection/ thrombosis	3,165
15	M	1	150	150	2	Not worked	675
16	MX4	4	170	43	1	None	549.3
17	MX4	4	300	75	4	Infection/ blocked	423.1
18	MX4	4	20	5	2	Blocked	311.9
19	MX4	4	19	5	3	Blocked	97
20	MX4	4	150	37	2	Blocked	Unknown
21	MX2, MX4, MX8	8	170	60	6	Blocked	854
22	M	4	250	60	5	Blocked	248

Key: *M* monthly, *MX2* twice per month, *MX3* three times per month, *MX4* four times per month, *MX6* six times per month, *MX8* eight times per month

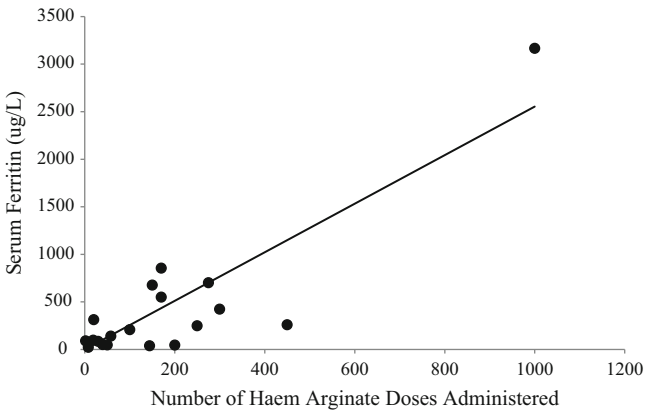

Fig. 1 Graph showing the correlation between the number of haem arginate vials and serum ferritin concentration

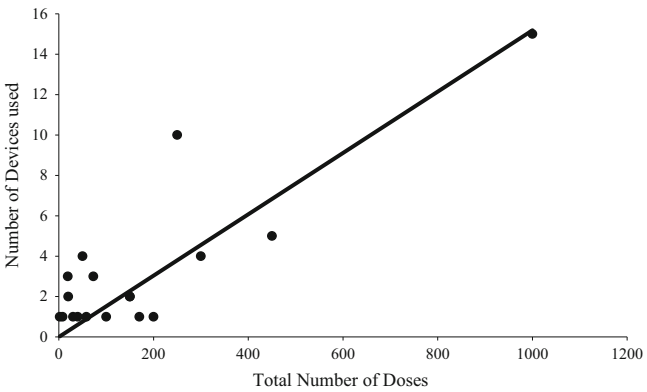

Fig. 2 Graph showing total number of doses of haem arginate and indwelling devices used

Table 4 Number of hospital admissions, acute attacks and co-morbidities before and during prophylaxis haem treatment

	Before prophylaxis				During prophylaxis				
Patient	Hospital admissions	Number of acute attacks	Number of years	Doses per year	Hospital admissions	No of acute attacks	Number of years	Doses per year	Co-morbidities
1	4	4	6	2	0	0	4 months	0	None
2	360	Acute symptoms	36	0	0	0	4	0	Depression
3	6	Acute symptoms	1	Unknown	0	0	2	0	Depression
4	Unknown	Unknown	Unknown	Unknown	35	35	8	4	None
5	5	5	2	10	15	15	3	5	None
6	6	6	3	8	0	0	7 months	1	None
7	7 months	15	1	60	0	0	5	0	None
8	4	4	32	<1	0	0	13	0	Renal impairment
9	5	5	2	10	1	1	1	1	None
10	20	20	6	13	11	11	11	1	Depression
11	140	140	7	80	63	63	11	6	Renal impairment
12	84	84	7	48	1	1	5	1	Depression
13	50	50	4	48	100	100	5	20	Renal impairment
14	60	60	4	75	28	28	14	2	Iron overload
15	18	18	9	8	0	0	10	0	Depression
16	12	12	2	24	0	0	4	0	None
17	50	50	4	50	7	7	7	1	None
18	12	12	1	48	10	10	2	5	Renal impairment depression
19	14	14	3	18	11	11	1	11	Depression
20	14	14	4	7	20	20	8	2	Renal impairment
21	Unknown	Unknown	6	Unknown	5	5	5	1	None
22	400	400	21	64	30	25	6	5	Renal impairment

Co-morbidities while the patients were on haem treatment included six patients (27%) with renal impairment and seven patients (32%) with depression. One patient had received a liver transplant and was not included in the study after the procedure.

Table 4 shows summary data on the patients detailing the hospital admissions, acute attacks and haem dosage before and during prophylactic haem treatment.

Stopping Prophylactic Haem Arginate Treatment

Six patients (27%) stopped prophylactic regular haem treatment, after a duration which varied from 8 months to 8 years. The reasons for stopping haem treatment are given in Table 5. Of the six who stopped treatment, prophylaxis had been effective in half.

Table 5 Reasons for stopping prophylactic haem arginate treatment

	Duration of treatment	Reason for stopping
1	2.5 years	Improved condition
2	13 years	Improved condition
3	5 years	Ineffective: liver transplant
4	8 months	Ineffective: treatment restarted
5	8 years	Improved condition
6	6 years	Loss of venous access

Discussion

Haem arginate (Normosang®) is usually administered at a dose of 3 mg/kg once daily for 4 days by infusions into a central vein delivered over at least 30 min. There is reasonable evidence for using haem arginate for patients having a single acute attack or infrequent attacks (Mustajoki et al. 1986; Kostrzewska et al. 1991). However, there is an important group of patients, predominantly as here women in the reproductive age group who have recurrent acute attacks usually requiring admission to hospital, opiate analgesia and emergency administration of haem arginate. These attacks severely disrupt home life, and many patients are no longer able to work; their quality of life is greatly impaired.

Although prophylactic haem is increasingly used, there is little or no published evidence to support its use to date. A recent observational study in the USA on patients with acute porphyrias using a different alkaline preparation (Panhematin®) reported that it had been effective in preventing recurrent attacks (Bonkovsky et al. 2014).

Our audit suggests that initiating regular haem arginate coincided with clinical improvement in 50–70% patients. There was an improvement in physical activity in 11 patients (55%), and 7 patients (35%) reported that their work attendance had improved. However there was still a requirement for regular analgesia with opiates in half of the patients, although 14 (67%) had fewer episodes of acute pain.

Suppression of menstruation is a therapeutic option in women with recurrent attacks, particularly if there is a link between the premenstrual period and acute pain. Seventy-one percent of the women in this audit had experienced GnRH agonists before starting haem therapy, although the hormonal intervention was ineffective in the majority. There are reports of beneficial effects of suppressing the menstrual cycle in some women, although these patients were unwilling to undergo treatment with regular haem arginate and were not included in this study.

As expected, we found a correlation between serum ferritin concentration and the number of haem arginate doses administered. However, in most cases, ferritin was only modestly elevated, and only one patient had unequivocal evidence of iron overload. This patient had received ~1,000 doses of haem arginate over a 10-year period; while there was hepatic iron loading, there was no evidence of cardiac iron loading on T2* magnetic resonance imaging. The pattern of iron loading in these patients was unusual, with relatively high serum ferritins associated with low or normal transferrin saturation, possibly reflecting the manner in which iron derived from paternally administered haem is metabolised.

The most frequent serious unwanted side effect concerned the loss of venous access, with an indwelling device typically lasting only 1–2 years. The main problem seems to be occlusion of the central catheter, and this appears to result from aggregation of haem arginate. Haem may also induce marked phlebitis and so activate local coagulation pathways leading to thrombus formation. One patient had to stop haem prophylaxis because of a complete loss of central and peripheral venous access, and another has already had 15 different semi-permanent venous access devices. Progressive damage to central veins is potentially serious and can preclude liver transplantation. The injurious effects on venous endothelium may be reduced by the use of albumin to dilute the haem arginate; while this is also an unlicenced procedure, it is the one adopted for nearly all the patients in this group.

Other important co-morbidities reported were renal impairment in six patients (27%); seven patients (32%) reported feeling depressed, and one patient had required a liver transplant. Renal impairment in patients, usually associated with hypertension and active porphyria, is well documented (Marsden et al. 2008; Frei et al. 2012). The causal factors are unclear although it may be due to toxicity of the precursor 5-aminolaevulinic acid or other haem precursors filtered in the urine that are formed in excess in the body during periods of activity; it is also possible in some patients that the effect is compounded by the use of nonsteroidal anti-inflammatory drugs. Depression is a prominent feature in patients with acute porphyria with seven patients (32%) reported feeling depressed during the period in which they were receiving treatment with prophylactic haem. No formal assessment was used, and it is not possible to assess from this retrospective audit data whether prophylactic haem arginate has any effect on co-morbidities such as depression or renal impairment.

Six patients stopped the treatment, and in three (50%) there were no further reported acute attacks, suggesting that prophylactic haem infusion is an effective long-term strategy in some, but not all, patients.

We noticed that stopping or reducing the frequency of haem arginate was difficult and associated with an exacerbation of symptoms in some patients. This “dependence”

has been plausibly linked to the induction of hepatic haem oxygenase-1 expression reported in healthy subjects (Doberer et al. 2010). Other studies have provided evidence of significant toxicity associated with intravenous haem, with induction of endothelial activation and a procoagulant state, and it is uncertain whether regular administration over many years is actually beneficial.

In the past, prophylactic haem arginate infusions were almost always administered in hospital through day-case admissions. However in the last 2 years, patients in England have been offered the alternative option of receiving haem arginate at home through a contracted homecare nursing provider as part of the National Acute Porphyria Service (NAPS). Twenty patients currently receive home infusions in this way. Our initial experience suggests that home treatment is safe, and there may even be a lower complication rate of vascular access, since home-care nurses work to a strictly agreed protocols and are experienced in administration techniques. Administration of haem arginate at home results in cost saving to the health service of up to 50% compared with hospital-based infusions. In addition, homecare allows more flexibility with infusion frequency and the potential for early treatment to avert acute attacks that would otherwise result in hospital admission.

In this study, few patients become symptom-free on prophylaxis, and only 14% were able to stop treatment successfully. This audit is retrospective and based on a small number of patients' experience with the use of prophylactic haem. For this reason, it is difficult to give any firm recommendations for treatment based on the findings so far. Prophylaxis seems to offer significant short- to medium-term benefit to more than half of the patients in this study with recurrent attacks. However, patients should be fully counselled about the potentially long-term nature of haem prophylaxis before starting, and potential side effects should be discussed. Ideally, prospective, randomised controlled trials are needed to address the value of prophylaxis, although the rarity of the condition makes this difficult.

Other therapeutic options for treating these patients are limited, and liver transplantation has been used with varying success. Dowman et al. 2012 reported a survival rate of 80% from UK Transplant Registry data collected between 2002 and 2010, but in that series, there was a high percentage of hepatic artery stenosis (40%). We consider that this procedure should be reserved for patients with severe recurrent acute attacks and greatly impaired quality of life.

Recent studies have shown that experimental targeting of 5-aminolevulinic acid synthase 1 (ALAS 1), the principal regulatory enzyme of haem biosynthesis in the liver by administering small interfering RNAs, is highly effective in preventing and aborting acute porphyric episodes in a mouse model of acute intermittent porphyria (Yasuda et al. 2014). Preclinical studies have been completed by Alnylam® Pharmaceuticals and phase I clinical studies are planned for 2015.

Synopsis

Prophylactic haem arginate treatment can be beneficial to patients with recurrent attacks of acute porphyria.

Compliance with Ethics Guidelines

Conflict of Interest

Joanne Marsden, Simon Guppy, Penelope Stein, Timothy Cox, Michael Badminton, Tricia Gardiner, Julian Barth, M Felicity Stewart and David Rees declare that they have no conflict of interest.

Informed Consent

This article does not contain any studies with human or animal subjects performed by the any of the authors.

Details on Contributions of Individual Authors

Joanne Marsden drafted and revised the article and analysed and interpreted the data.

Simon Guppy was involved in the design of the audit, collated and analysed the data and had input into revision of the article.

Penelope Stein was involved in the design of the audit, collated data and had input into revision of the article.

Timothy Cox was involved in the design of the audit, collated data and had input into revision of the article.

Michael Badminton was involved in the design of the audit, collated data and had input into revision of the article.

Tricia Gardiner was involved in the design of the audit, collated data and had input into revision of the article.

Julian Barth was involved in the design of the audit, collated data and had input into revision of the article.

M Felicity Stewart was involved in the design of the audit, collated data and had input into revision of the article.

David Rees was involved in the design of the audit, collated and analysed data and had input into the revision of article. He is Guarantor for the article.

References

Anderson KE, Spitz IM, Bardin CW, Kappas A (1990) A gonadotropin releasing hormone analogue prevents cyclical attacks of porphyria. Arch Intern Med 150(7):1469–1474

Bonkovsky HL, Maddukuri VC, Yazici C et al (2014) Acute porphyrias in the USA: features of 108 subjects from porphyria consortium. Am J Med. doi:10.1016/j.amjmed.2014.06.036

Doberer D, Haschemi A, Andreas M et al (2010) Haem arginate infusion stimulates haem oxygenase-1 expression in healthy subjects. Br J Pharmacol 161:1751–1762

Dowman JK, Gunson BK, Mirza DF, Badminton MN, Newsome PN (2011) UK experience of liver transplantation for erythropoietic protoporphyria. J Inherit Metab Dis 34(2):539–545

Dowman JK, Gunson BK, Mirza DF et al (2012) Liver transplantation for acute intermittent porphyria is complicated by a high rate of hepatic artery thrombosis. Liver Transpl 34:195–200

Elder G, Badminton M, Harper P, Sandberg S, Deybach JC (2013) The incidence of inherited porphyrias in Europe. J Inherit Metab Dis 36(5):849–857

Frei P, Minder EI, Corti N et al (2012) Liver transplantation because of acute liver failure due to heme arginate overdose in a patient with acute intermittent porphyria. Gastroenterology 6 (1):190–196

Herrick AL, McColl KE, Moore MR, Cook A, Goldberg A (1989) Controlled trial of haem arginate in acute hepatic porphyria. Lancet 10(1):1295–1297

Kostrzewska E, Gregor A, Tarczynska-Nosal S (1991) Heme arginate (Normosang) in the treatment of attacks of acute hepatic porphyrias. Mater Med Pol 23(4):259–262

Ma E, Mar V, Varigos G, Nicoll A, Ross G (2011) Haem arginate as effective maintenance therapy for hereditary coproporphyria. Australas J Dermatol 52(2):135–138

Marsden JT, Chowdhury P, Wang J et al (2008) Acute intermittent porphyria and chronic renal failure. Clin Nephrol 69(5):339–346

Mustajoki P, Tenhunen R, Tokoa O, Gothoni G (1986) Haem arginate in the treatment of acute hepatic porphyrias. Br Med J (Clin Res Ed) 293:538–539

Puy H, Gouya L, Deybach JC (2010) Porphyrias. Lancet 375:924–937

Sardh E, Wahlin S, Bjornstedt M, Harper P, Andersson DE (2013) High risk of primary liver cancer in a cohort of 179 patients with acute hepatic porphyria. J Inherit Metab Dis 36(6):1063–1071

Soonawalla ZF, Orug T, Badminton MN et al (2004) Liver transplantation as a cure for acute intermittent porphyria. Lancet 363:705–706

Stein PE, Cox TM (2011) Homecare delivery of haem arginate in acute porphyria International Porphyrins and Porphyrias Meeting, 10-14 April 2011, Cardiff, UK. Br J Dermatol 164:1125–1176

Stein P, Badminton M, Barth J, Rees D, Stewart MF (2013) Best practice guidelines on clinical management of acute attacks of porphyria and their complications. Ann Clin Biochem 50:217–223

Yasuda M, Gan L, Chen B et al (2014) RNAi-mediated silencing of hepatic Alas 1 effectively prevents and treats the induced acute attacks in acute intermittent porphyria mice. Proc Natl Acad Sci U S A 111(21):7777–7782