An Audit of the Use of Gonadorelin Analogues to Prevent Recurrent Acute Symptoms in Patients with Acute Porphyrria in the United Kingdom

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Abstract Severe recurrent acute attacks of porphyria have traditionally been treated with either prophylactic human haemin or gonadorelin analogues (GnA) in females. Evidence on the most effective treatment for this patient subgroup is lacking. This audit surveyed the use of prophylactic GnA in the UK.

Twenty female patients (who experienced between 2 and 45 acute attacks of porphyria requiring hospitalisation and treatment with human haemin prior to GnA prophylaxis) were included in the audit. Data was retrospectively collected based on patient history and case review.

Twenty three treatment courses were given lasting a median period of 12 months. Monthly subcutaneous Goserelin was most commonly used. In three patients in whom timing with the menstrual cycle was not considered, an acute attack occurred after initiation of the first dose. The majority of patients experienced oestrogen deficiency symptoms during treatment. Fifty percent of the prescribed courses of GnA resulted in a degree of clinical benefit. This

successfully treated group experienced between 3 and 20 acute attacks prior to and between 0 and 6 acute attacks during GnA treatment.

The audit revealed large variation in practice in the United Kingdom regarding indication, duration of treatment, specific drug used and management of side effects. In view of the limited treatment options available for this cohort and the mixed outcome successes reported, we believe it is reasonable for porphyria specialists to continue offering GnA treatment to women with severe recurrent debilitating acute attacks of porphyria associated with the menstrual cycle, and we propose best practice guidelines to standardise management.

Introduction

The porphyrias are a group of mainly inherited conditions that result from a partial deficiency of one of the enzymes in the haem production pathway. The eight different porphyrias are characterised by either acute neurological and/or cutaneous symptoms and signs, depending on which enzyme is affected and the resultant pattern of toxic haem precursor build-up proximal to the metabolic block. Three autosomal dominant porphyrias cause acute neurological symptoms: acute intermittent porphyria (AIP), variegate porphyria (VP) and hereditary coproporphyria (HCP).

During an acute attack the majority of patients experience severe abdominal, back or thigh pain, other features of autonomic neuropathy such as vomiting, constipation, hypertension and tachycardia, behavioural disturbances (Peters and Sarkany 2005) and an increase in urine porphobilinogen (PBG) excretion. Treatment includes providing symptomatic relief including carbohydrate and

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administering intravenous human haemin (haem arginate Normosang®, Recordati, Paris) (Stein et al. 2013). Haem, the final product of the pathway, suppresses the rate limiting first enzyme, 5-aminolaevulinic acid synthase 1 (ALAS1). Provision of exogenous haem down-regulates the pathway with a decrease in toxic precursor build-up and resolution of symptoms.

A small proportion of patients, particularly those with AIP, develop recurrent debilitating attacks (Elder et al. 2013). Frequent hospital admissions have a devastating impact on their quality of life. In women these recurrent attacks are often associated with the luteal phase of the menstrual cycle; symptomatic disease usually resolves following the menopause.

Published evidence on the most effective way to manage this challenging patient subgroup is lacking. Prophylactic haem has been used for the last two decades to prevent or decrease the frequency of acute attacks (Stein and Cox 2011; Marsden et al. 2015). Liver transplant has been effective in a few cases (Soonawalla et al. 2004), but is used as a last resort (Dowman et al. 2012). For repeated pre-menstrual acute attacks, an alternative option is pituitary ovarian suppression using gonadorelin analogues (GnA) (Anderson et al. 1984), which down-regulate ovarian oestrogen and progesterone production, the likely triggers of acute attacks. Previously hormonal manipulation with oral contraceptive agents had been used successfully (Perloth et al. 1965). However in view of the risks associated with exogenous sex hormone therapy (Andersson et al. 2003) this is no longer pursued as a treatment option.

The aim of this audit was to review the historic and varying practices in the use of GnA in females with severe recurrent acute attacks of porphyria in the UK, and where possible, to use this data together with existing evidence to develop a preliminary guide to aid patient management. These standards could subsequently be used for future prospective audit.

Method

Patients were identified through the UK National Acute Porphyria Service (NAPS) database, which was established in 2012 to manage patients with active acute porphyria and currently includes two expert and two outreach centres. Of the 135 patients followed up by NAPS, 62 were defined as having current or previously active recurrent porphyria. Amongst these patients, 20 were identified for inclusion in the audit who had been treated with GnA between 2000 (prior to the establishment of NAPS) and 2015. An audit proforma (Table 1) was created to enable the collection of data on the particulars of GnA administration and distributed to all centres. The questionnaire was retrospec-

tively completed by the clinicians and/or specialist nurses with clinical responsibility for the patient based on patient history and case review and returned between September 2014 and May 2015.

An acute attack was generally defined as an acute worsening of porphyria symptoms which local clinicians had decided required admission to hospital. The historic, retrospective nature of the data collected precluded the use of a more specific definition.

The questionnaire included a question to both the patient and the responsible clinician to state whether in their view GnA was successful, partially successful or unsuccessful in reducing acute attack frequency without predefined quantitative outcome measures.

Results

Pre-GnA Treatment

Twenty female patients with repeated acute attacks of porphyria received GnA prophylaxis (Table 2), 18 of whom had AIP, 1 with VP and 1 with HCP. The age of diagnosis (genetic confirmation in 18 and biochemical diagnosis in 2 patients) ranged between 17 and 41 years and the age of the first acute attack was between 19 and 41 years.

First acute attack precipitants were documented as unsafe drugs in eight patients, menstrual cycle related in two patients, dieting in two patients, pregnancy in one patient, stress in one patient, the menstrual cycle and a drug in one patient, alcohol and drugs in one patient and in four patients a precipitant was not identified.

The number of hospital admissions and courses of symptomatic haem arginate treatments ranged between 2 and 45 and the number of Intensive Treatment Unit (ITU) admissions between 0 and 1. Only one patient had received prophylactic haem arginate prior to GnA which was ineffective in preventing recurrent attacks.

GnA Treatment

Twenty three courses of prophylactic GnA were administered to 20 patients (Table 2); patient 1, 14 and 15 received a second course. The median duration of a treatment course was 12 months and ranged between 1 and 54 months. The drug most commonly used was Goserelin (17/23 courses), 4 patients received Leuprorelin and 1 Triptorelin. For patients in whom this information was available most received the drug administered monthly subcutaneously. Three patients received either Leuprorelin or Goserelin every 3 months. No patients received intranasal preparations.

In only 6 of the 17 (35%) treatment courses for which this information is known, was the GnA treatment started in

Table 1 Audit proforma

Demographics	
Diagnosis	
Pre-GnA treatment	Age of first acute symptoms, precipitants, total number of acute attacks, hospital/ITU admissions prior to GnA, evidence of neuropathy, regular analgesia requirement, previous prophylactic human haemin, co-morbidities, QOL assessment
During GnA treatment	Analogue, route, frequency and duration of treatment, timing of the dose in terms of menstrual cycle, adverse event with first dose, side effects with continued use, monitoring of bone density, oestrogen replacement, total number of hospital/ITU admissions for acute symptoms, evidence of neuropathy, regular analgesia need, QOL assessment, judgment of whether GnA was deemed successful or not
Post-GnA treatment	Occurrence of further attacks, number of hospital/ITU admissions, need for human haemin, evidence of neuropathy, QOL assessment

GnA gonadorelin analogue, ITU intensive treatment unit, QOL quality of life

the recommended first few days of the follicular phase of the menstrual cycle (Anderson 1989; BNF 2013). In none of these 6 treatment courses did initiation of GnA precipitate an acute attack. In total three acute attacks occurred after initiation of the first drug dose and in all three cases GnAs were not given during the first week of their cycle. In patient 1 in whom a first dose acute attack was precipitated, the same drug was subsequently reintroduced during the first week of the cycle without adverse effect.

Patients experienced oestrogen deficiency side effects in 16 of the 19 treatment courses for which this information is known. The majority reported hot flushes but a minority also described hair thinning (two patients), mood changes (three patients) and reduced libido (one patient). Seven patients received hormone replacement therapy which included oestrogen only, tibolone or combined oestrogen and progesterone preparations to treat symptoms. Bone mineral density was monitored in 9 of the 23 treatment courses ranging between 4 and 54 months. The treatment courses in which bone mineral density was not monitored ranged from 1 to 25 months. Information on bone mineral density measurements and whether hormone replacement therapy precipitated any acute attacks or not was insufficiently reported in the majority of patients on the returned audit forms.

The patient receiving Triptorelin had only recently been initiated on treatment, and outcome data was therefore not available. Of the remaining treatment courses, 8/22 (36%) were deemed by the patient and responsible clinician as successful with regard to reducing acute attack frequency, 3/22 (14%) as partially successful, 8/22 (36%) as unsuccessful and for 4/22 (18%) this information was not stated (Table 3). A quantitative definition of treatment success was unfortunately not predefined, but both the patient and clinician were asked their opinion on whether a clinical improvement in terms of reduction in acute attack frequency and therefore quality of life was achieved or not.

In the 11/22 (50%) successful or partially successful courses, patients were treated with either Goserelin or Leuprorelin. Of the eight patients in whom treatment was deemed a success, the initial precipitant was drugs in four, menstrual cycle one, menstrual cycle and a drug one, fasting/dieting one and unknown in one patient. Eight patients experienced between 3 and 20 attacks pre GnA and between none and 6 acute attacks whilst on GnA with no ITU admissions documented. Six patients completed their treatment course which was stated as lasting between 16 and 54 months. One patient discontinued treatment after 3 months due to unacceptable oestrogen deficiency side effects but deemed it as successful as she had no acute attacks during the 3 months; and one patient discontinued treatment at 12 months as she had the desire to conceive.

In the partially successful group (3/22), drugs or drugs and alcohol was the initial precipitant of symptomatic disease in all three cases. In this group one patient had no further attacks for 3 months (vs. 6 admissions pre-treatment) after which GnA was stopped when she underwent a hysterectomy and oophorectomy, one patient had 2 further attacks (baseline number of attacks unknown) and GnA was stopped after 9 months and 1 had treatment for 10 months during which she had only 1 attack (vs. 5 attacks pre-treatment) which was stopped due to unacceptable side effects.

Of the eight patients in whom the treatment was deemed unsuccessful, only one patient's symptomatic disease was assessed as associated with the menstrual cycle. She had 10 attacks pre-treatment, was treated for 24 months during which she had a further 4 acute attacks and suffered unacceptable side effects.

In patient number 1 an acute attack occurred after the first dose of Goserelin, as mentioned this was reintroduced and continued for 16 months and deemed as successful. Patient number 14 had a first course lasting 4 months which was deemed unsuccessful as she had a further 5 attacks, then had a second course over 36 months, the success of

Table 2 Patient demographics prior to and during GnA treatment

Demographics			Pre-GnA		GnA treatment							
Patient	1st attack age (years)	Diagnosis	Precipitant ^a	Acute attack hospital admissions ^b	Nr of haem courses for acute attacks	Prophylactic haem	Analogue	Frequency/route	Duration ^c	Timing ^d	First dose adverse event	E deficiency side effects
1	23	AIP	Drug	>6	U	N	Goserelin	Monthly SC	1	N	Acute attack	N
1							Goserelin	Monthly SC	16	Y	N	Y
2	21	HCP	Drug	6	3	N	Leuprorelin	Monthly SC	3	N	U	N
3	25	AIP	Drug	3	3	N	Leuprorelin	3 monthly SC	24	Y	N	Y
4	27	AIP	Drug	U	U	NS	Goserelin	Monthly SC	9	Y	N	Y
5	19	AIP	Drug	>3	2	N	Goserelin	Monthly SC	24	Y	N	Y
6	41	AIP	Dieting	9	7	N	Goserelin	Monthly SC	U	N	N	NS
7	26	AIP	U	28	28	N	Goserelin	Monthly SC	U	U	U	NS
8	27	AIP	U	2	2	N	Goserelin	Monthly SC	4	Y	N	Y
9	19	AIP	Drug	45	45	N	Goserelin	Monthly SC	12	NS	N	Y
10	19	AIP	U	13	6	N	Triptorelin	NS	Ongoing	N	Acute attack	Y
11	19	AIP	Drug	10	10	Y	Leuprorelin	Monthly SC	10	Y	N	N
12	18	VP	Menstrual cycle/drug	4	3	N	Leuprorelin	Monthly SC, later switched to 3 monthly	25	U	N	Y
13	Mid teens	AIP	Menstrual cycle	10	10	N	Goserelin	Monthly SC	24	N	Flushing, nausea, hypotension	Y
14	20	AIP	Second pregnancy	>5	U	N	Goserelin	Monthly SC	4	N	N	Y
14							NS	NS	36	U	N	NS
15	22	AIP	Drug	NS	1	N	Goserelin	Monthly SC	36	U	U	NS
15							Goserelin	NS	54	U	N	Y
16	22	AIP	Alcohol/drug	5	5	N	Goserelin	Monthly SC	10	N	N	Y
17	23	AIP	U	15–20	15–20	N	Goserelin	Monthly SC	12	N	N	Y
18	28	AIP	Dieting	5	5	N	Goserelin	Monthly SC	3	N	N	Y
19	22	AIP	Menstrual cycle	5–10	5–10	N	Goserelin	Monthly SC, later switched to 3 monthly	42	N	N	Y
20	21	AIP	Stress	4	4	N	Goserelin	Monthly SC	5	N	Acute attack	Y
Median ^e (range)	22 (19–41)			(2–45)	(2–45)				12 (1–54)			

NS not stated on returned audit questionnaire, U unknown, N no, Y yes, SC subcutaneous, Nr number, E oestrogen

^a Precipitant of first acute attack^b Total number of acute attacks only; time intervals not documented^c Duration in months^d Whether administered in first week of menstrual cycle^e Calculated from the known data only

Table 3 Outcome

Deemed as successful	Patient	Number of pre-GnRH acute attack admissions	Precipitant of symptomatic porphyria	Analogue used	Duration in months	Number of acute attack admissions on GnRH	Reason for withdrawal
Y	1	>6	Drug	Goserelin	16 (unsure)	NS	Completed 16 months
Y	3	3	Drug	Leuprorelin	24	1	Completed 24 months
Y	5	>3	Drug	Goserelin	24	1	Completed 24 months
Y	12	4	Menstrual cycle/drug	Goserelin	25	0	Completed 25 months
Y	15	U	Drugs	Goserelin	54	1	Completed 54 months
Y	17	15–20	U	Goserelin	12	1	Wanted to conceive
Y	18	5	Dieting	Goserelin	3	0	Side effects
Y	19	5–10	Menstrual cycle	Goserelin	42	3–6	Completed 42 months
PS	2	6	Drug	Leuprorelin	3	Y ^a	Hysterectomy with oophorectomy
PS	4	U	Drug	Goserelin	9	2	Further attacks
PS	16	5	Alcohol/drugs	Goserelin	10	1	Side effects
N	20	4	Stress	Goserelin	5	1	Further attacks
N	1 (a second treatment course)	>6	Drug	Goserelin	1	NA ^b	Triggered attack
N	6	9	Dieting/fasting	Goserelin	U	8	Further attacks
N	8	2	U	Goserelin	4	1	Further attacks Side effects
N	9	45	Drug	Goserelin	12	12	Further attacks
N	11	10	Drug	Goserelin	10	3	Further attacks
N	13	10	Menstrual cycle	Goserelin	24	4	Side effects
N	14	>5	Second pregnancy	Goserelin	4	5	Further attacks
NS ^c	7	28	U	Goserelin	U	Y ^a	NS
NS ^c	14 (a second treatment course)	>5	Second pregnancy	NS	36	NS	NS
NS ^c	15 (a second treatment course)	U	Drugs	Goserelin	36	NS	Completed 36 months
NA ^c	10	13	U	Triptorelin	Ongoing	1	NA
	Median of known data (range)	(2–45)			12 (1–54)		

U unknown, NA not applicable, NS not specified, Y yes, PS partly successful, N no

^aNumber not specified on returned proforma

^bWas in hospital for an acute attack when GnA was initiated and experienced a further attack whilst still in hospital

^cFor patient 7, 14 and 15 (one of the two treatment cycles they received) information on whether the treatment was deemed successful or not was not documented on the returned proforma. As patient 10 had not completed the treatment course an opinion on whether it was successful or not was not given on the returned proforma

this or number of attacks was not specified. Patient number 15 had a first course of treatment lasting 36 months which was not well documented and a second course lasting 54 months, deemed as successful during which she only had 1 acute attack.

Information on analgesia requirements and quality of life prior to and during GnA prophylaxis was not sufficiently complete to report.

Following completion of prophylactic GnA treatment 17 patients have subsequently experienced further acute attacks, 5 of whom had had >4 acute attacks at the time the audit was conducted.

Discussion

Acute attacks of porphyria in AIP, HCP and VP are clinically similar and potentially life threatening. There are a variety of known physiological and environmental triggers that precipitate acute attacks. Drugs, steroid hormones, alcohol, fasting and infection directly or indirectly via cortisol and other hormones induce nuclear receptor activation resulting in either hepatic ALAS1 induction or cytochrome P-450 (haem containing) enzyme production needed for drug metabolism or hormone synthesis (Badminton et al. 2012). The influence of steroid hormones such as oestrogen and progesterone and differences in gender control of pituitary axis regulation explains why symptomatic acute porphyria is more common in women than men and why in women recurrent attacks may be associated with the menstrual cycle (Badminton et al. 2012; Thunell 2006), particularly in AIP (Hift and Meissner 2005).

GnA prophylaxis for prevention of menstrual cycle associated acute attacks was first described in 1984 (Anderson et al. 1984). Prior to this, hormonal manipulation to suppress ovulation with oral contraceptives was used with limited success (Perlroth et al. 1965). GnA initially acts as an agonist, but when administered continuously, desensitises the pituitary to GnA action with decreased pituitary LH and FSH release and suppression of ovulation and ovarian hormone production.

This retrospective audit demonstrates a large variation in practice in the United Kingdom with regard to prophylactic GnA treatment for females with recurrent acute porphyria attacks. Between 2000 and 2015, 23 treatment courses of GnA were given to 20 females with recurrent acute attacks over a period ranging between 1 and 54 months with a median treatment period of 12 months. Monthly subcutaneous Goserelin was most commonly used. In only 3 of the 20 patients treated with GnA was the initial precipitant of the first acute attack thought to be hormonal changes associated with the menstrual cycle. However 50% of the

prescribed courses of GnA were viewed as being of clinical benefit in reducing acute attack frequency. The successfully treated group experienced between 3 and 20 acute attacks prior to and between 0 and 6 acute attacks during GnA treatment.

Published case studies and series (Anderson et al. 1984; Herrick et al. 1990; Innala et al. 2010) demonstrated that menstrual cycle associated acute attacks usually occur in the luteal phase, prior to menstruation when mid cycle oestrogen surges and corpus luteum progesterone production occurs, with symptoms subsiding with the onset of menstruation as hormone levels fall. As a result it has been recommended that prophylactic GnA should be initiated in the first week of the menstrual cycle (Anderson 1989; Herrick et al. 1990), when the risk of precipitating an acute attack is the lowest, although the evidence to support this is anecdotal. The efficacy of GnA is believed to be due to the down-regulating and resistance of pituitary receptors to hypothalamic LH releasing hormone (Fraser and Baird 1987). In the six treatment courses in which this timing was adhered to, no acute attacks were precipitated. In 3 of the 17 courses for which the timing of the dose was not considered, an acute attack occurred after administration of the first dose, suggesting that it may be the safest to initiate treatment in the first week of the menstrual cycle.

GnA renders females post-menopausal and predictable side effects include oestrogen deficiency symptoms such as hot flushes, bone demineralisation (Studd and Leather 1996) and reduced libido. Pregnancy is contraindicated during treatment, and patients should be advised about alternative contraceptive methods. Intra-nasal, subcutaneous or intramuscular preparations are available. Patients in this survey were all treated with long acting subcutaneous preparations administered monthly apart from three patients who received it 3 monthly. Both of these approaches were successful in reducing acute attack frequency. Eleven of the 16 patients with documented oestrogen deficiency side effects reported hot flushes and a minority also described low mood, hair thinning and loss of libido. Hormone replacement therapy using oestrogen or progesterone or both has been used previously with some patients experiencing reactivation of their porphyria (Innala et al. 2010). Reluctance to prescribe hormone replacement therapy to alleviate these symptoms exists due to both the fear of precipitating an acute attack and the requirement for endometrial monitoring, as evident by only seven patients receiving hormone replacement for symptomatic relief. This demonstrates that post menopausal symptoms are very common using prophylactic GnA and patients need to be fully informed prior to treatment which may improve successful completion of treatment courses.

Other methods of ovulation prevention using oral contraceptives (combined or progesterone alone) have not

been successful in the past as acute attacks have been precipitated in a subgroup of symptomatic patients (Anderson et al. 2003; Innala et al. 2010; Lamon et al. 1979; Levit et al. 1957; Edwards and Elliot 1975; Kappas et al. 1968).

The retrospective nature of this audit has significant limitations. Data quality is subject to recall bias as it relied on the accurate recording of clinical information and patient recollection. We have chosen to not report information where there were doubts over the accuracy. Data comparing symptoms, neuropathy, need for analgesia between attacks, quality of life measures prior to and during GnA prophylaxis and detailed information on bone mineral density monitoring and hormone replacement regimes were too incomplete to report. The quantitative criteria for what would be considered a successful treatment outcome were not predefined and relied on patient and clinician opinion on whether clinical improvement on GnA with regard to decreasing acute attack frequency occurred. In the absence of complete remission of acute attacks, many courses were reported as unsuccessful or partially successful despite a clear improvement in patient symptomatology. Without an exact successful outcome definition, the occurrence of side effects could also have influenced the outcome opinion.

Despite these shortcomings, this is the first attempt at auditing the use of prophylactic GnA for recurrent acute attacks of porphyria in females in the United Kingdom, the majority of treatment having occurred prior to the establishment of a nationally commissioned and governed service. The audit reveals large variation in practice with regard to indications for and duration of GnA treatment as well as monitoring and treatment of side effects necessitating a more unified approach and identifying the need for treatment guidelines despite the existing limited evidence.

Three previous case series using GnA in 27 patients in total have been reported with similar partial success rates (Anderson et al. 1990; Herrick et al. 1990; Innala et al. 2010). Including our audit, a degree of clinical benefit with regard to reducing acute attack frequency has been reported in 31 of the 47 patients described. In a prospective study of 7 women between the age of 22 and 35 (Herrick et al. 1990), buserelin 4 times a day intranasally was given for 12 months. Reduction in acute attack frequency was reported in 5 females and the authors concluded that clinical benefit was dependent on the strength of the association between attack onset and stage of the menstrual cycle. In another cohort of 14 females (Innala et al. 2010) treated with either intranasal, subcutaneous or intramuscular buserelin or triptorelin for between 5 months and 9 years, 11 reported the treatment as beneficial with 4 having almost no further attacks. The third cohort (Anderson et al. 1990) treated 6 females for up to 26 months and benefit was observed in 5.

All three cohorts reported oestrogen deficiency side effects, predominantly flushing and vaginal dryness in the majority of patients. In the one case series (Innala et al. 2010), hormone replacement therapy induced recurrence of attacks in 7 of 11 patients receiving oestrogen alone or in combination with progesterone. This group monitored the endometrium with 6-monthly uterine ultrasound and endometrial sampling. In agreement with our audit there was a lack of systematic consideration of the effect of this treatment on bone health in all three series.

Conclusion

Randomised control trial data on the efficacy of GnA and comparison of GnA versus prophylactic human haemin in preventing recurrent acute attacks of porphyria in females are lacking. Similarly to the case series' previously published, this audit demonstrates mixed results with regard to acute attack prevention in females with acute porphyria. Approximately 50% of the prescribed courses of GnA in our audit resulted in some degree of subjective clinical benefit although clear outcome criteria were not defined which makes judging success rates difficult. In view of the limited treatment options available for this challenging patient cohort and the mixed outcome successes reported, we believe it is reasonable to continue offering GnA treatment to women with recurrent debilitating attacks of acute porphyria, particularly if the attacks are clearly associated with the menstrual cycle, and the first dose is given in the first week of the cycle. GnA treatment is generally less complicated to deliver than regular haem arginate, which requires insertion of a semi-permanent venous access device and repeated, usually weekly, intravenous administration with the accompanying risks of extravasation, infection, malfunction and potential for iron overload.

The audit also demonstrates large variation in practice in the United Kingdom with regard to the indication for GnA use, duration of treatment, specific drug used and degree of monitoring and treatment of side effects. Based on the experience of this patient cohort and review of the limited literature, we suggest the following best practice guidelines to standardise the management of this subgroup of severely affected acute porphyria patients. These can also be used as standards for future NAPS prospective audit.

Indication for Prophylactic GnA Treatment

1. Confirmed recurrent acute attacks (≥ 4 per year) of sufficient severity to require hospitalisation and treatment

with human haemin and which are associated with increased urine PBG excretion.

2. Females in whom acute attacks are associated with the menstrual cycle. A decision to embark on preventative treatment with GnA should always be reached in partnership with the patient after thorough, candid discussion of the likely benefits and risks.

Treatment

3. A multidisciplinary approach should be adopted between a clinician with expertise in porphyria and a gynaecologist with experience in the use of GnA. In the United Kingdom this should be through the NAPS service.
4. The first dose should be given during day 1–5 of the menstrual cycle.
5. The risk of precipitating an acute attack appears low and therefore it is reasonable for prophylaxis to be initiated on an outpatient basis.
6. Both intranasal and subcutaneous (monthly or 3 monthly) depot preparations appear to be successful in reducing acute attack frequency. Depot preparations may be preferred by patients compared to nasal preparations that require several doses daily.
7. To date, our largest experience has been with monthly subcutaneous Goserelin injections.
8. Patients should be monitored monthly for efficacy and side effects during the early phase of treatment, and then 6-monthly if treatment is continued
9. In view of the natural history and possibility of disease remission, treatment duration should be for a maximum of 2 uninterrupted years.

Side Effects and Monitoring

10. Oestrogen deficiency side effects occur in the majority of women and patients should be informed regarding this prior to initiating treatment.
11. Contraceptive advice should be provided as anovulation is not guaranteed and unwanted pregnancies whilst on GnA prophylaxis have been described (Innala et al. 2010).
12. Bone mineral density should be determined pre-treatment and then annually whilst GnA treatment is continued (Herrick et al. 1990).
13. Ensure all patients are Vitamin D replete prior to commencement of GnA prophylaxis; adequate dietary calcium intake and Vitamin D supplementation is recommended.

Withdrawal of Treatment

14. Case studies and case series demonstrated that the benefit is not always immediate so withdrawal due to treatment failure should only be considered after 3 months of no apparent benefit.
15. After completing 2 years of prophylactic GnA. If acute attacks recur, then a further treatment course can be considered, subject to confirmation of satisfactory bone mineral density.

Take Home Message/Synopsis

Although no trial data exists, prophylactic GnA may be a reasonable alternative to prophylactic human haemin in women with severe recurrent attacks of acute porphyria, particularly where attacks are associated with the menstrual cycle.

Compliance with Ethics Guidelines

Conflict of Interest

Danja Schulenburg-Brand, Tricia Gardiner, Simon Guppy, David C. Rees, Penelope Stein, Julian Barth, M. Felicity Stewart and Michael Badminton declare that they have no conflict of interest.

Informed Consent

Not applicable as this was an audit.

Animal Rights

Not applicable.

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

Author Contributions

Danja Schulenburg-Brand: data analysis and authored the paper.

Tricia Gardiner: audit design, data collection and review of paper.

Simon Guppy, David Rees, Penelope Stein, Julian Barth, Felicity Stewart: review of audit design, data collection and review of paper.

Mike Badminton: audit design, data collection and co-authored the paper.

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