Insights into Proton Pump Inhibitor-induced photosensitivity

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Title: Insights into Proton Pump Inhibitor-induced photosensitivity: An observational study in a tertiary photobiology service

Shortened Title: Proton pump-induced photosensitivity

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ABSTRACT

Background: Proton pump inhibitors (PPIs) are extensively prescribed but may cause photosensitivity and drug-induced lupus erythematosus (DILE), which can be over looked as the drug may have been taken for years prior to presentation.

Methods: We reviewed the clinical and investigation findings of patients diagnosed with PPI-induced photosensitivity, diagnosed through the Scottish Photobiology Service.

Results: We report 11 patients with median age of onset 61-years and mean duration of PPI ingestion of 5-years [DILE(n=6), phototoxicity(n=3) and drug-induced solar urticaria through a lupus mechanism(n=2)]. Five had Anti-Ro antibodies (3 also ANA positive). Predominantly UVA and visible light photosensitivity was observed on phototesting.

Discussion: PPIs are a reversible cause of photosensitivity and DILE. Time to onset from drug initiation to symptoms can be prolonged, so clinicians should have a high index of suspicion in those taking PPIs. Most are diagnosed through clinical assessment and lupus serology, with phototesting indicated if there is diagnostic uncertainty.

INTRODUCTION

Proton pump inhibitors (PPIs)can cause a range of dermatological adverse effects, including photosensitivity disorders, encompassing drug-induced lupus erythematosus (DILE) and phototoxicity (DIP).[1,2]DILE can be particularly difficult to distinguish from idiopathic cutaneous lupus given the similarities between the two entities clinically, histopathologically and immunologically.[1]Additionally, the insidious delayed onset presentation after drug commencement adds to the diagnostic challenge, as a drug cause may not be considered unless identified by clinicians who are aware of this possible association.

We have noted a diverse range of clinical manifestations of PPI-induced photosensitivity (an abnormal reaction to light quantitatively and/or qualitatively when compared with the background Scottish population reference range[2]) in patients diagnosed through the Scottish Photobiology Service (SPS), which is a tertiary photodiagnostic service. We therefore wished to characterise in detail the phenotypic patterns of the various presentations of PPI-induced photosensitivity and to report on the outcomes of photodiagnostic investigations of this patient cohort. Given the ubiquitous prescription of PPIs[3] we considered that it was important to raise awareness of these potential cutaneous adverse effects of PPIs to clinicians and patients, in order to minimise over-prescribing of this drug class and to emphasise the importance of early recognition, as drug cessation is largely curative.

METHODS

Patients who had an initial diagnosis of probable PPI-induced photosensitivity who were seen through the SPS, a tertiary photodiagnostic service hosted in Dundee, prior to January 2020were identified through our photobiology and dermatology in-house databases and were considered for inclusion in this study. The search terms used were PPI, photosensitivity, omeprazole, lansoprazole, esomeprazole, rabeprazole, pantoprazole, drug-induced photosensitivity. Hospital case notes, blood test results and photobiology investigation findings for all patients identified were then retrieved and

reviewed. Data were anonymised and recorded in an excel spreadsheet. Caldicott Guardian approval (IGTCAL8206) was obtained prior to undertaking the study.

There was subsequent refinement of the original patient cohort through categorisation of patients into five different tiers of diagnostic likelihood of PPI-induced photosensitivity: definite -testing on the drug showed photosensitivity and repeat phototesting off the drug confirmed photosensitivity resolution; probable - phototesting confirmed photosensitivity, unable to confirm by repeat testing off the drug; highly possible - photosensitivity reaction certain, although unclear if the reaction was idiopathic or due to PPI; possible - alternative diagnoses possible; doubtful - other diagnoses confirmed. Only patients with definite, probable and highly possible diagnoses were included in this study.

Photoinvestigations undertaken on these patients included phototesting, which was carried out on the back using a monochromator device (Bentham, Reading UK) with dose-series at UVB, UVA and visible wavebands (305±[half maximum bandwidth]5nm, 335±27nm, 365±27nm, 400±27nm and430±27nm).[4]Erythemal responses (minimal erythema doses; MEDs) were assessed immediately and at 7 and 24 hours and compared with our background normal population range.[2]

RESULTS

Patient demographics and clinical features

Of the 25 patients who were initially identified as having probable PPI-induced photosensitivity, 11 patients in the period 2014 to 2016 fulfilled the criteria for definite, probable and highly possible diagnostic likelihood of PPI-induced photosensitivity and were investigated further. Nine patients were female and two were male (Table 1). Median age of onset was 61 (range 43-77) years and median age on presentation to the SPS for investigation was 67 (range 48-78) years. Mean duration of ingestion of the suspected causative PPI was 5(range 1.5-12) years. The average dermatology life quality index (DLQI) score at presentation was 13 (range 2-25), indicating a very large adverse impact

on quality of life.[5]The most common features reported were skin reddening (erythema) (n=11, 100%), itch (pruritus) (n=6, 50%), swelling (oedema) (n=4, 33%) and papules (n=3, 25%).Six patients presented with a clinical presentation of drug-induced lupus, three with drug-induced phototoxicity and two with drug-induced solar urticaria relating to a lupus mechanism.

Duration of sunlight exposure required for rash triggering varied from 5 minutes to several hours and time to onset of symptoms after exposure varied from 5 minutes to 24 hours. Time to resolution of symptoms varied from 30 minutes once provoked to 24 hours, and time to resolution from stopping the drug was up to three years. All patients reported involvement of photo-exposed skin sites, with most reporting only involvement of sunlight exposed skin (n=8) (Figures 1a & b, a violaceous photo-distributed lichenoid eruption and monochromator phototesting showing UVA sensitivity at 24 h and just extending up into the visible part of the spectrum (400-430nm)), and the remaining three patients reporting involvement of both exposed and non-exposed skin sites. Two patients reported the phenomenon of hardening (Table 1, Patients 3 and 9). Six noticed development of symptoms following light exposure through clothing, five patients noted symptoms following exposure to sunlight transmitted through window glass and one developed symptoms when exposed to artificial lighting.
The most commonly prescribed PPI was omeprazole (n=6), followed by lansoprazole (n=3) and finally rabeprazole (n=1) and pantoprazole (n=1). Most patients were prescribed a PPI for gastroesophageal reflux disease (n=6), followed by gastritis or oesophagitis (n=2), Barrett's oesophagus (n=1), hiatus hernia (n=1) and for gastroprotection (n=1).

Investigations

Blood tests were performed in all 11 patients (Table 1). Two patients had evidence of lymphopenia, although none had thrombocytopaenia or neutropenia. Five patients had detectable anti-Ro antibodies (Table 1, patients 1, 4,6,7 and 11). All of the six patients who were tested for anti-histone antibodies (Patients 2, 3, 6, 9, 10 and 11), the four patients tested for lupus anti-coagulant (Patients 4-7) and four tested for cardiolipin antibodies had negative results (Patients 4-7).

Three patients had detectable antinuclear antibody (ANA) at 1:640 (Patients 1,6 and 11). Of those who were anti-Ro and ANA positive, one had a drug-induced solar urticaria presentation, another an Subacute Cutaneous Lupus Erythematosus-like (SCLE-like) presentation and the final had an SCLE-like presentation as well as discoid lupus. Two patients who were only Anti-Ro positive had an acute lupus erythematosus-like presentation. No patients had evidence of elevated double-stranded DNA antibodies. Nine patients had complement levels checked (Patients 2-9 and 11), and these were all normal.

Six patients had skin biopsies performed, one of which was undertaken at their referring hospital and was summarised as in keeping with lupus (Patient 1). One patient's biopsy was in keeping with chronic dermatitis (Patient 8). Of the remaining four patients, all had evidence on skin biopsy of lymphocytic infiltrates in either the perivascular space, epidermis or peri-appendageal; one also had evidence of mucin deposition (Patient 10), another evidence of hyperkeratosis and vacuolar alteration of the basal cell layer (Patient 6). Immunofluorescence was requested in five biopsies and all were negative.

Monochromator phototesting was carried out on all patients. Testing was normal in three patients, all of whom were not tested while they were taking the suspected PPI. In the remaining eight patients, the most prominent pattern seen on phototesting was delayed sensitivity to ultraviolet A and visible light (Figure 2; Table 1, for specific testing results), with some having UVB sensitivity. Additionally, two patients developed immediate urticarial reactions on phototesting to wavebands 335-600 nm (Patient 1) and 305– 400nm (Patient 3).

Management

All patients were advised to follow careful sun avoidance measures, including behavioural and environmental advice and use of photoprotective clothing and high factor (SPF 50) sunscreens. Furthermore, all were advised to discontinue their PPI and switch to a histamine-2(H_2) receptor

antagonist, where feasible. Four patients were discharged to their local dermatologists for further follow-up and management. Four patients underwent repeat phototesting, with one of these patients having a reduction in sensitivity on repeat phototesting off the PPI, although the same action spectrum (wavebands affected) was involved (Patient 1). Another patient was unable to stop the suspected culprit PPI for longer than a month due to severe gastritis symptoms. They reported an improvement in their symptoms during the period off the PPI, however repeat phototesting was carried out after the PPI was reinstated and showed the same levels of photosensitivity (Patient 3). Another patient was able to come off the PPI prior to repeat phototesting and showed resolution of their photosensitivity (Patient 4). The final patient who underwent repeated phototesting appeared less sensitive on repeat phototesting after cessation of the PPI, however subjectively they reported full resolution of their symptoms following fundoplication for treatment of their gastroesophageal reflux disease (Patient 10). Two patients had gastric fundoplication (Table 1, Patients 4 & 10). This allowed them to stop PPIs and their photosensitivity subsequently resolved.

DISCUSSION

PPIs are a widely prescribed class of medications, used not only to treat gastroesophageal reflux disease but also for gastric protection whilst taking concomitant gastric irritant medications. In 2017, omeprazole and lansoprazole were the 3rd and 8th most commonly prescribed drugs in England respectively, with their combined prescriptions totalling approximately 56 million.[3]Given their widespread use, it is imperative that clinicians are aware of the potential complications that may arise from this drug class. PPIs may cause a range of cutaneous adverse reactions, some of which are more significant than others. Hypersensitivity reactions of varying degrees can occur with PPIs, including urticaria/angioedema and anaphylaxis, vasculitis, acute allergic interstitial nephritis, erythroderma, drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome, Stevens-Johnson syndrome, toxic epidermal necrolysis and autoimmune reactions such as lupus erythematosus.[6] Furthermore, it has become apparent during the SARS-CoV-2 pandemic, that patients taking PPIs who

were infected with COVID-19 were almost twice as likely to have severe disease and a poorer outcome.[7]

PPIs have also been identified as an emerging cause of immunologically mediated photosensitivity disease, in the form of drug-induced lupus, with reports particularly highlighting the subacute cutaneous lupus erythematous type as most common.[1,8] PPI-induced lupus may also present as phototoxicity with an exaggerated sunburning tendency. Additionally, whilst anti-nuclear antibodies and anti-Ro antibodies are most likely to be positive, both should be included in serological testing as both are not always consistently positive, as we showed with our patients, where only three of the five patients who were Ro positive were also ANA positive. Anti-histone antibodies are less helpful in this condition with low positive serology noted in multiple observational studies, as well as in our case-series.[8]

We saw a variety of clinical manifestations of PPI-induced lupus erythematosus that have not been reported elsewhere, including two patients with suspected drug-induced solar urticaria relating to a lupus-like mechanism, and additionally tumid lupus and an acute cutaneous lupus erythematosus reaction. Biopsy findings in our series also showed changes in keeping with lupus erythematosus. On phototesting, we predominantly noted a delayed UVA and visible light photosensitivity, consistent with other photoactive drug sensitisers. UVB photosensitivity was also seen in the minority, which whilst documented with some drug photosensitisers, is less typically seen in drug-induced photosensitivity.

Despite its recognition as a distinct entity, differentiating drug-induced lupus from idiopathic lupus is challenging due to similarities in clinical features, histopathology and immunological findings.[1] Delay in diagnosis is compounded by the insidious and delayed presentation of symptoms from the time of starting the PPI, and therefore a high index of suspicion of this potential drug adverse effect is necessary. Cessation of the drug is usually curative. Failure to suspect the diagnosis may put patients

at risk of additional iatrogenic harm from use of immunosuppressive therapy if patients are then managed based on a diagnosis of autoimmune lupus erythematosus. Counselling patients regarding awareness of this as a possible adverse effect may also alert them to symptoms earlier and prevent more severe disease presentation, particularly if photoprotective measures are routinely employed.

PPIs have also increasingly been associated with non-immunological phototoxic reactions[9] whereby the drug is the chromophore within the skin that is activated by particular wavelengths of ultraviolet light, which then produces metabolites or oxygen radicals, in turn causing direct tissue damage.[10] Typical clinical features include the acute easy or exaggerated sunburn reaction of erythema and oedema, as well as a prickling or burning sensation on sun exposure. Some patients may also report delayed erythema with hyperpigmentation. Once again, drug cessation is typically curative, although it may take many months for the photosensitivity to resolve.[10]

Drug cessation can be challenging for those with refractory gastric symptoms, particularly in the current climate of limited availability of H_2 antagonists. In our cohort, it is worthwhile noting that two patients with severe gastric symptoms when off a PPI, underwent gastric fundoplication and following this had total resolution of their photosensitivity once their PPI was able to be withdrawn. This reminds us that surgery is a reasonable therapeutic alternative to consider for those with severe gastro-oesophagitis who develop intolerable photosensitivity due to PPIs.

PPIs are a reversible cause of photosensitivity and cutaneous lupus. Given the widespread prescribing of this drug class it is important that clinicians are aware of this potential adverse effect, facilitating avoidance of over-prescribing of this drug class and allowing prompt recognition and appropriate patient counselling and management. It is also important to emphasise that this adverse effect may present at a late stage after years of PPI ingestion. This highlights the need for in-depth medicines reconciliation when taking a history in those with a photosensitivity or cutaneous lupus presentation, in order to avoid missing PPIs as a cause of their dermatological presentation.

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Patient	Diagnosis / Drug	Age / Gender	Site	Clinical features	Positive blood results	Testing on PPI	Monochromator testing	Management	Follow up
1	Drug induced solar urticaria relating to a lupus mechanism /Lansoprazole	67/F	Face, neck, hands	Erythema, oedema & pruritus	Anti-Ro 28(0-10) ANA 1:640	Yes	335nm – 600nm immediate urticaria	PPI stopped& trialled H_2 antagonist Photoprotection*	Repeat phototesting on ranitidine – 335nm to-430nm – immediate urticaria – improved sensitivity but no change in action spectrum Antibodies remained positive
2	Drug induced lupus (SCLE) /Omeprazole	77/M	Chest, arms, forearms and upper back	Erythema, scale & pruritus	Nil relevant	No	305nm – 430nm Normal	PPI stopped Photoprotection*	Discharged
3	Drug induced solar urticaria (possibly lupus mechanism) /Omeprazole	48/F	All sites	Erythema, oedema, pruritus	Nil relevant	Yes	305nm - 400nm immediate urticaria	PPI stopped Photoprotection* Positive rechallenge	Repeat phototesting on omeprazole– 305-430nm immediate urticaria Subjective improvement off drug (1 month)
4	Drug induced lupus (acute) /Pantoprazole	57/F	Face, neck	Erythema & Oedema	Anti-Ro 101(0-10)	Yes	305nm, 365nm + 400nm abnormal delayed sensitivity	PPI stopped Photoprotection* Positive dechallenge** Fundoplication	Resolution of symptoms following cessation of PPI & sustained after fundoplication Repeat phototesting off drug – normal
5	Drug induced phototoxicity /Omeprazole	73/F	Face, neck	Erythema, pruritus & oedema	Nil relevant	Yes	Delayed 365nm abnormal delayed sensitivity	PPI stopped Photoprotection*	Positive dechallenge**, resolved after stopping PPI for 4 months Discharged
6	Drug induced lupus (SCLE) /Omeprazole	78/F	Neck, face and arms	Erythema, papules, pruritus	Plasma viscosity 1.85(1.5-172) Anti-Ro >240(0-10) ANA 1:640	No	305nm – 430nm Normal	PPI stopped Photoprotection*	Assumed positive dechallenge** from clinical history, phototested off PPI at presentation
7	Drug induced lupus (acute) /Omeprazole	57/F	Face, neck, anterior thighs	Erythema & oedema	Anti-Ro 188(0-10)	No	305nm - 430nm Normal	PPI stopped Photoprotection*	Discharged

8	Drug induced phototoxicity /Lansoprazole	64/M	Face & arms	Erythema	Nil relevant	Yes	365nm delayed sensitivity, 335nm + 400nm borderline delayed sensitivity	PPI stopped & started ranitidine 300mg BD Photoprotection*	Positive dechallenge** – resolved after 3 years
9	Drug induced lupus (lupus erythematous tumidus) /Lansoprazole	52/F	Lateral arms, back all over exp upper, ant chest.	Erythema, papules, pruritus	Nil relevant	Yes	365nm abnormal delayed sensitivity, 400nm borderline sensitivity	PPI stopped & trialled ranitidine Photoprotection*	Discharged
10	Drug induced phototoxicity /Rabeprazole	73/F	Scalp, neck, lower lip	Erythema	Lymphocytes 1.3 $x10^{9/L}$	Yes	335nm-430nm abnormal immediate (maximal at 7 hours, fading by 24) and less severe delayed sensitivity	PPI stopped & trialled ranitidine Photoprotection* Partial positive dechallenge** Fundoplication	Repeat phototesting – 335-460nm abnormal delayed sensitivity, less sensitive compared to previous readings Resolution of symptoms following cessation of PPI after fundoplication
11	Drug induced lupus (SCLE and discoid) /Omeprazole	68/F	Arms, forearms, backs of hands, upper back, anterior upper chest and face	Erythema & papules	Lymphocytes 1.3 $x10^{9/L}$ Anti-Ro 253(0-10) ANA 1:640	Yes	365nm - abnormal delayed sensitivity	PPI stopped Photoprotection* including window film to block UVA light	Discharged

Table 1. Clinical features and phototesting results of patients with PPI induced photosensitivity.
*Photoprotection advice includes behavioural and environmental advice as well as protective hats, clothing &high SPF sunscreen use.
**Positive dechallenge refers to recovery from the drug side effects following discontinuation of the medication

Figure Legends

Figure 1a: An erythematous lichenoid eruption on photo-exposed sites of the chest. Note the sparing under the chin and on the covered sites of the chest (Patient 2).

Figure 1b: An erythematous lichenoid eruption on the photo-exposed sites of the dorsal hand, forearm and upper arm. Note sparing of the distal phalanges as these sites tend to be hidden from the sun while in a relaxed position of partial flexion. Note also sparing of the upper arm under clothing (Patient 2).

Figure 2. Abnormal monochromator phototesting. This patient presented with suspected PPI-induced photosensitivity and phototesting showed abnormal photosensitivity in the UVA and visible part of the spectrum (335-430 nm) (Patient 10).