Urticaria flare: an unusual factor limiting glycaemic control

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Introduction

Controlling hyperglycaemia is essential for reducing the risk of diabetes-related complications,[1] but hypoglycaemia is a recognised consequence of blood glucose-lowering therapy.[2,3] Rapid lowering of blood glucose has been reported to cause dermatological manifestations, such as urticaria, in addition to autonomic and neuroglycopaenic symptoms.[4]

It is known that use of oral hypoglycaemic agents and insulin is associated with various side effects including skin manifestations.[5–7] Local hypersensitivity reactions are well reported with insulin treatment and drug eruptions have been reported with metformin.[8] To date there are no reports of worsening of urticaria related to treatment with insulin and oral hypoglycaemic agents, other than in the setting of acute hypoglycaemia.

We present here a case of recurrent flare of urticaria with the introduction of several hypoglycaemic agents (oral and injectable).

Case report

A 46 year-old Caucasian male was referred to the diabetes clinic for management of his type 2 diabetes. This was diagnosed when he presented to his general practitioner with symptoms of polyuria and was found to have a fasting blood glucose of 14.5 mmol/L.

His past medical history included urticaria, angioedema and childhood asthma, but no other autoimmune disorder. His urticaria was controlled using treatment with ranitidine 150 mg twice daily, levocetrizine 5 mg once daily and montelukast 10 mg once daily. Asthma was well controlled with a salbutamol inhaler used as required, with no requirement for regular inhaled steroids.

He worked as a plasterer, having worked as a plastics injector. His urticaria presented four years prior to the development of diabetes, associated with intermittent swelling of the lips, eyes, tongue and hands. These symptoms occurred infrequently and not all together. He was reviewed by the dermatologist and testing revealed slightly elevated IgE and allergy to grass and house dust mite. C1 esterase deficiency was excluded. Cetirizine 10 mg daily initially reduced his symptoms but after 6 months this was changed to levocetirizine 5 mg daily and ranitidine 150 mg twice daily. Over the next 6 months he continued to have breakthrough flare of urticaria. Montelukast 10 mg daily was commenced and provided good symptom control. He was discharged from regular dermatology review and remained on this treatment combination until after his diabetes diagnosis.

Gliclazide and metformin were prescribed following the diagnosis of diabetes. There was a good antihyperglycaemic response with this combination therapy, but he suffered a flare of urticaria, which persisted despite stopping metformin but settled completely after stopping gliclazide. He refused to have a retrial with either metformin or gliclazide and was referred to the hospital diabetes clinic, where he was prescribed pioglitazone. Three months of this treatment also produced a good lowering of blood glucose, but he discontinued pioglitazone following a further flare of urticaria. Exenatide was started as an alternative but unfortunately had similar effects: reduction in blood glucose with worsening urticaria. He was monitoring his capillary blood glucose and there was no record of hypoglycaemia.

He was reviewed again by the dermatologists at our request. They were of the opinion that, although metformin and other hypoglycaemic agents have been reported to cause drug eruptions, flare of urticaria was not recognised or reported as a side effect of any of the oral hypoglycaemic agents. By this stage, he was reluctant to have any treatment for diabetes but agreed to a trial with insulin, specifically glargine titrated up to 20 units as per a standard titration protocol. This improved his blood glucose readings but again coincided with worsening of his urticaria. He stopped insulin but was persuaded to restart at a low dose of 2 units with very slow (1 unit/week) titration. His fasting glucose dropped from 12–16 mmol/L to 8 mmol/L over a period of five months without a flare of his urticaria. We then added metformin to his insulin glargine (now at a dose of 45 units).

The glargine dose was then gradually reduced at the patient's request as he wished to try managing his diabetes without insulin. Later, gliclazide was reintroduced. He successfully managed this transition without a further flare of urticaria for 6 months and was returned to the care of his primary care physician.

Abbreviations and acronyms

CRH Corticotrophin releasing hormone

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Table 1 Changes in treatment, HbA_{1c} and urticaria over time

Date	Treatment	HbA_{1c} (%)	Comment)
On diagnosis	Diagnosis	10.4	
At 2 months	Gliclazide and metformin	8.7	Urticaria flare
At 5 months	Pioglitazone	8.5	Urticaria flare
At 7 months	Exenatide	9.1	Urticaria flare
At 10 months	Glargine small dose	11.2	No flare-up
At 15 months	Glargine 45 units	8.9	No flare-up
At 18 months	Gliclazide and metformin	8.7	No flare-up

Discussion

This is the first report of flare-up in urticaria caused by multiple diabetes treatments. We postulate that this was due to reduction in blood glucose and hence tissue glucose levels, rather than hypersensitivity to the various hypoglycaemic agents involved. Hypoglycaemia induces marked cortisol and adrenaline release, which ordinarily would ameliorate urticaria. It is paradoxical, therefore, that this patient had a flare-up of urticaria each time his hyperglycaemia improved.

Sacerdote provided one possible explanation for this response, in 1987.[4,9] Urticaria, bronchospasm and rhinitis are all atopic manifestations that are precipitated by environmental cold. A drop in body temperature associated with hypoglycaemia may have a similar effect on the body as environmental cold, causing urticaria. Webster and colleagues suggested another possible mechanism.[10,11] CRH is an immunomodulatory peptide that causes peripheral vasodilatation and also increases both vascular permeability and mast cell degranulation in a dose dependent fashion. Incubation of mast cells with specific primers for the mast cell CRH-R1 receptor resulted in the release of polymerase chain reaction products consistent with mast cell degranulation. Given that CRH is secreted by postganglionic sympathetic neurons as well as the hypothalamus, both of which are activated during hypoglycaemic stress, CRH-stimulated mast cell degranulation could result in a flare-up of urticaria.

Previous reports have demonstrated cutaneous side effects from glucose lowering medication,[6,7] so it is possible that our patient had a flare in urticaria as a result of side effects from all of the agents listed. It is also possible that his chronic urticaria became less problematic with time, of its own accord. The temporal relationship we saw between periods of glucose lowering and increased flare of urticaria, however, would suggest change in glucose control did indeed provoke flare in his urticaria (see Table 1).

Conclusion

Flare-up of pre-existing urticaria is a poorly-recognised side effect of glucose lowering by any modality. If this occurs, as demonstrated in our patient, the flare-up can be mitigated by cautious and gradual reduction in blood glucose. This is probably best achieved by using insulin in the first instance, with transfer at a later stage to oral therapy.

Key messages

- Urticaria may be precipitated by glucose lowering treatment
- This effect may occur regardless of the type of glucose lowering treatment utilised
- Urticaria flare may be mitigated by a controlled, gradual reduction in glucose and this is probably best achieved using insulin initially

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References

1. UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet* 1998;**352**:854-65. http://dx.doi.org/10.1016/S0140-6736(98)07037-8
2. Towler DA, Havlin CE, Craft S, Cryer P. Mechanism of awareness of hypoglycaemia: perception of neurogenic rather than neuroglycopenic symptoms. *Diabetes* 1993;**42**:1791-8. http://dx.doi.org/10.2337/diab.42.12.1791
3. Cryer PE. Hypoglycemia, functional brain failure, and brain death. *J Clin Invest* 2007;**117**:868-70. http://dx.doi.org/10.1172/JCI31669
4. Sacerdote A. Urticaria as a sign of hypoglycaemia (Letter). *Diabetes Care* 1987;**10**:257. http://dx.doi.org/10.2337/diacare.10.2.257a
5. Antidiabetic drugs. *British National Formulary 59* 2010; 6.1.1:403-414.
6. Shadid S, Jensen MD. Angioneurotic edema as a side effect of pioglitazone. *Diabetes Care* 2002;**25**:405. http://dx.doi.org/10.2337/diacare.25.2.405
7. Almeyda J, Baker H. Drug reactions. X. Adverse cutaneous reactions to hypoglycaemic agents. *Br J Dermatol* 1970;**82**:634-7. http://dx.doi.org/10.1111/j.1365-2133.1970.tb06111.x
8. Antidiabetic drugs. *British National Formulary 59* 2010; 6.1.2: 414-417.
9. Sacerdote AS. A reply (Letter). *Diabetes Care* 1988;**11**:440-41. http://dx.doi.org/10.2337/diacare.11.5.440b
10. Webster E, Papanicolau DA, Boucher W, *et al*. The mast cell as a target of peripheral "immune" corticotropin-releasing hormone (CRH) and mediator of its pro-inflammatory properties: clinical implications (Abstract). The Endocrine Society, 77th Annual Meeting, Program and Abstracts, 1995; p. 280
11. Theoharides TC, Singh LK, Boucher W, *et al*. Corticotropin-releasing hormone induces skin mast cell degranulation and increased vascular permeability, a possible explanation for its proinflammatory effects. *Endocrinology* 1998;**139**:403-13. http://dx.doi.org/10.1210/en.139.1.403