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CASE REPORT

A Common Event, Occurring for Some Uncommon Reason

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Introduction

Hypoglycemia is a very common event, but often a dreaded one for its immediate and far reaching complications. Presentations may be widely varying from a subtle behavioural change to convulsions and deep coma, from which there may be permanent brain damage, if sufficiently prolonged. In a general term, a blood sugar level below 63 mg % is accepted as a hypoglycemic level, though it is variable from person to person, particularly depending on his average glycemic level.

To brand a patient as having a hypoglycemic disorder one must confirm "Whipple's triad", which has three components. Firstly, the patient must be having symptoms of hypoglycemia, secondly, low blood glucose level at the time of the symptoms and thirdly, the symptoms must be resolved on correction of hypoglycemia.

Hypoglycemia is always a foreseen complication of Diabetics, particularly for those who are on insulin and / or sulfonyl ureas. Usually the patient, physician and their family members are aware and cautious of the event and are expected to know the basics of home management. It is the non-diabetics where hypoglycemia, if ever occurs, poses a real threat as everyone is unprepared and it may be difficult to find the aetiological diagnosis.

To be brief we may divide the conditions causing hypoglycemia in non-diabetic individuals (spontaneous hypoglycemia) into three groups:

A) Drugs: of which Ethanol is the commonest, particularly after an alcoholic binge. Others are salicylates, quinine, chloroquine, pentamidine, ACE inhibitors, Angiotensin receptor blockers, quinolones (anti infectives), indomethacin, sulfonamides and proton pump inhibitors (prazoles). These are mentioned in common text and reference books [1, 2]

B) Systemic conditions, namely hepatic, renal or cardiac failure, adrenal insufficiency, hypothyroidism, pan hypopituitarism, sepsis, malaria (both vivax and falciparum) and malignant tumours, particularly abdominal ones and sarcomas are also known the cause for hypoglycemia.

C) Insulin secreting tumours (insulinomas) of pancreas or other tumours which secrete insulin like substances.

Our Patient and His Presentation

P.B, a male aged 64, non-diabetic, non-hypertensive had been complaining of prostatism for last one decade. He was on Tamsulosin 0.4 mg/day for last 5 years, but regularly for last 2 years or so. Recently since the month of April 2014 he had been complaining of right testicular swelling and tenderness. USG of scrotum and its contents showed an epididymitis with a small hydrocele on the right side. He was afebrile, his urine culture was sterile and his blood counts were normal. He did not respond satisfactorily to an empirical exhibition of levofloxacin for three weeks and was thought to have a reflux epididymitis.

In June 2014, Alfuzosin was added to make the alpha-blockage more complete. His testicular symptoms

improved remarkably, but soon he started feeling very weak and run down in morning and afternoon, which gradually worsened. In the third week of July, he started having tremors in early morning and late evening and was nauseated which he ascribed to weakness. On 24th July 2014, he had a sudden palpitation early morning and thought it to be due to bad dreams. In evening, at his office, he noticed a double vision, some difficulty in speaking and writing. Sensing a disaster, he retired to his bed where he fell deeply unconscious shortly.

He was rushed to a nursing home in the neighbourhood, where his Capillary Blood Glucose (CBG) was 31mg% and venous blood glucose was 34 mg%. He was resuscitated with usual measures like 25% Dextrose IV and regained consciousness and orientation within two hours. In spite of continuous glucose infusion and carbohydrate rich diet his blood sugar was not more than 100mg% in the next 36 hours.

His routine blood count, urea, creatinine, potassium, sodium, morning cortisol, TSH, ECG all were absolutely normal. On the morning of 26th July, 2014 serum Insulin and C-peptide were assayed and both were in the lower half of normal range, while his blood sugar (CBG) at that moment was around 100mg%. Initial blood sample during admission was not tested for insulin and C–peptide and the standard challenge test with 72 hrs near fasting was not attempted. His CECT Brain and abdomen revealed no abnormality, particularly endocrine tumours of pancreas were sought for.

All previous medications (alpha-blockers) were withdrawn from the day of admission and he was discharged on 27th July. CBG was closely monitored and was found to be in the range of 70 – 100mg, in spite of a carbohydrate rich diet. It took almost ten days for the CBG to reach the standard 80 – 130 mg% level.

Finding no obvious reasons to explain the hypoglycemia, references were searched regarding the possibility of inducing hypoglycemia by Tamsulosin and Alfuzosin. Standard text and reference books gave a list of medicines causing hypoglycemia in non diabetic people but those two were not mentioned. Internet based research [3,4] yielded two amazing results :

1. The website, www.eHealthMe.com, based on data compiled from FDA on 14.7.2014, reports a 0.89% incidence of hypoglycemia with Tamsulosin. It states to have the highest incidence of hypoglycemia (75%) when patients have been using it for 2–5 years and of them 95% are above 60 yrs. Results are quite matching with that of our patient.
2. In the same portal, based on FDA data on 20.7.2014, Alfuzocin showed a 0.54% incidence of hypoglycemia but all of the patients are recent users and all of them and are in the 50–60+ age group. Though the number is very small, these data also match our case. Similar comments were found in Medfacts. com after a meta-analysis.

Discussion

Mr P.B, 64 years had been on regular Tamsulosin for the last 3 years, and has added Alfuzosin over and above it and the near fatal hypoglycemia occurred approximately after a month. Possibly the hypoglycemic effects of both became additive. Both these net references were not very clear and assertive about the nondiabetic status of the patients having hypoglycemia, though it seems to be implied.

The purpose of citing this problem is to underscore the point that many of the oft-prescribed medicines might produce side effects yet unknown, rare but dangerous for which mind must be open.

As an epilogue we may mention three more points.

1. Being confused and not believing in hypoglycemic potential of the two alpha blockers, Tamsulosin 0.2mg/ day was restarted (not with Alfuzocin) as urinary symptoms reappeared. Weakness and tremulousness reappeared after 4–5 days with a morning CBG of 65mg%. Tamsulosin was then stopped and Naftopidil (50mg daily), another alfa blocker was started. He is now asymptomatic urologically and without any hypoglycemic symptom with Naftopidil.
2. To the best of efforts no clear explanation or hypothesis regarding the mechanism of production of hypoglycemia by those two agents is available. However, the scanty literature, whatever available may suggest alpha blockers may either block the glucagon receptors or may partially block release of glucagon from alpha cells of pancreas. But it needs more experiments and observations.
3. Several α1-blockers are clinically available, including those having nonspecific affinity for á1receptor subtypes (Prazosin, Terazosin, Doxazosin, Alfuzosin) and those having specific affinity for them (Tamsulosin, Naftopidil, Silodosin). Three types of α1receptor subtypes are identified like α1A, α1B, α1D of which α1A, α1D are expressed in prostatic tissue. The tissue of Benign Prostatic Hypertrophy shows nine- and

threefold increased expression of mRNA of á1A and á1D-AR subtypes respectively, compared to normal prostatic tissue[5]. Naftopidil has three times greater affinity for á1D than for the á1A-receptor subtype compared to Tamsulosin, and is an á1-blocker for clinical use for Lower Urinary Tract Symptoms/Benign Prostatic Hypertrophy.[6] It may be hypothesised that the non-appearance of hypoglycemia with Naftopidil may be due to this receptor difference.

Conclusion

Many elderly persons, with or without diabetes, are suffering from prostatic problems and alfa blockers are prescribed. Majority of them are also having renal compromise. As such the clinician should mentally be alert about the development of hypoglycemia. If alfa blockers are added on existing antidiabetic regimen, a clinician should also keep in mind that whether the latter need any down titration in terms of dose in near future. Of course the firm opinion will develop after large experiences of usage of the drug and awareness.

References

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"It is better to change an opinion than to persist in a wrong one."
— Socrates