The highs and lows: A case of drug-induced beta cell dysfunction

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Background

Corticosteroids and asparaginase are standard chemotherapy agents in Acute Lymphoblastic Leukaemia (ALL) protocols worldwide. Hypergylcaemia is a well-recognised side effect of these agents, particularly during induction therapy[1-3]. Hypoglycaemia following asparaginase administration has rarely been documented[4-5].

We present a case of drug-induced hyperglycaemia and subsequent hypoglycaemia following pegasparaginase and dexamethasone administration during ALL induction chemotherapy.

Drug	Adverse effect and mechanism
Corticosteroids	• **Hyperglycaemia-** insulin resistance and gluconeogenesis[1]
Asparaginase	• **Hyperglycaemia**- insulin deficiency[2,3] • **Hypoglycaemia**-insulin hypersectretion[4-5]

Table 1: Mechanisms of drug-induced beta cell dysfunction

Case presentation

A 21-month old female with newly diagnosed ALL was treated with induction chemotherapy as per Children's Oncology Group (COG) high-risk protocol AALL1131. Induction chemotherapy included:

- High-dose oral dexamethasone (5mg/m^2) on days 1-14
- Intravenous (IV) pegasparaginase (2500 IU/m^2) on day 4
- Other chemotherapy agents administered were intrathecal (IT) cytarabine, IT methotrexate, IV daunorubicin and IV vincristine.

The events that occurred during the initial induction period are outlined below:

Day -2
- Dexamethasone commenced

Day 1
- Vincristine and daunorubicin administered
- Urine glucose negative

Day 4
- Pegasparaginase administered
- Urine glucose remains negative

Day 6
- Presence of urinary glucose +++, negative ketones, random blood glucose level (BGL) 25mmol/L, sodium 129 mmol/L
- Drug-induced diabetes diagnosed
- Diagnosis complicated by co-administration of dexamethasone and pegasparaginase
- Basal-bolus insulin regimen commenced (initially actrapid 0.5 units/exchange, 0.3 units/ correction and Lantus 3 units BD, titrated to response)

Day 12-15
- Hypoglycaemic events began occurring despite reduction in insulin
- Insulin ceased on day 15

Day 16-21
- Hypoglycaemic events continued despite insulin cessation and with 10% and 15% glucose infusions
- Additional glucose boluses were also required

Day 22
- Diazoxide commenced to treat hypoglycaemia at a starting dose of 20mg TDS (5mg/kg/day)

Day 23
- Persistent hypoglycaemic events occurred despite diazoxide initiation
- Diazoxide dose increased to 40mg TDS (10mg/kg/day)

Management and outcomes

- For the management of hypoglycaemia, diazoxide was initiated due to its hyperglycaemic effects
  - Diazoxide is not licenced in Australia and was sourced through the Special Access Scheme (SAS)
  - Capsules were manufactured into a 10mg/mL liquid.
- Beta cells appeared to be slowly recovering as blood glucose levels (BGLs) stabilised
  - Diazoxide slowly reduced to a current dose of 25mg TDS
  - Mucositis and acute illness during interim maintenance had affected blood sugar levels and prevented any further reductions in diazoxide dose.
- Pharmacy were consulted for the optimal oral glucose requirement and suitable glucose sources for a 21-month old for management of BGLs <3mmol/L
  - Apple juice was used initially but volume requirements (100mL) resulted in poor tolerability
  - Honey sachets and glucose powder were suitable alternatives.
- Various factors have been considered during the ongoing management of this patient:
  - Planned hospital admissions are required for monitoring while fasting prior to lumbar puncture procedures
  - Planning and management of subsequent exposure to pegasparaginase. Further pegasparaginase was required during consolidation and will again be necessary in the upcoming delayed intensification protocol.

A multidisciplinary approach

The management of this case involved multidisciplinary input from paediatric oncology/haematology, paediatric endocrinology and pharmacy.
Consultation with these teams allowed for:

- Control of hyperglycaemia and subsequent hypoglycaemia
- Obtaining and titrating diazoxide
- Chemotherapy planning for lumbar punctures and subsequent pegasparaginase administration
- Education to family for BGL monitoring and management particularly around pegasparaginase doses.

Discussion

- The initial hyperglycaemia in this patient was induced by the concomitant administration of dexamethasone and pegasparaginase[1-3].
- Pegasparaginase was considered the causative agent for the patient's subsequent hypoglycaemia. This was based on the proposed mechanism of pegasparaginase causing hyperinsulinism and the lack of other identifiable causes.
- Unfortunately, critical bloods to confirm hyperinsulinism was inconclusive due to the patient being in a normoglycaemic state at the time of testing. The test has not since been repeated as BGLs have remained stable.
- Corticosteroids are known to mask hypoglycaemic effects. Concurrent use could possibly explain the lack of reported incidences of asparaginase-induced hypoglycaemia[3,4].
- Pegasparaginase was administered twice during consolidation treatment as an outpatient. Management during this time is outlined below:
  - Diazoxide stopped at the first pegasparaginase infusion with education provided to parents for BGL monitoring
  - BGLs remained stable until 48 hours after the infusion. Hypoglycaemia began to occur and diazoxide was re-started at the same dose
  - There was no interruption or changes to diazoxide therapy during the second infusion and BGLs remained stable
  - Corticosteroids were not a part of therapy during the consolidation phase.
- Pegasparaginse is required a further two times during delayed intensification. Dexamethasone will be administered concurrently during the first infusion. The patient will be closely observed during this time.

Conclusion

Chemotherapy adverse effects can cause many challenges during ALL treatment. This case highlights a rare situation of drug-induced hyperglycaemia and hypoglycaemia during induction chemotherapy and the management for unavoidable subsequent drug exposure.

References

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