TOXICOLOGY: AN AUSTRALIAN PERSPECTIVE

Toxicology case of the month: oral hypoglycaemic overdose

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A teenager ingests 375 mg of glipizide and 14.5 g of melformin intentionally in a small country town. She presents to the local medical facility with symptoms and signs of hypoglycaemia. Using a risk assessment based approach, the management of suiphonylurea and metformin overdose is discussed. Sulphonylurea overdose invariably results in profound hypoglycaemia that requires resuscitation with IV dextrose and the use of octreotide as an antidote. Metfonnin overdose rarely causes problems.

This is the first in a series of cases presented by the Western Australian Toxicology Service. The cases are selected for their relevance to emergency medicine practice and emphasise the importance of risk assessment in formulating a coherent management plan for the acutely poisoned patient (boxes 1 and 2). These principles were discussed in depth in the introductory article for this series.[1]

PATIENT DETAILS

A 15 year old female presents to the hospital of a small remote town 2600 km north east of Perth. Some 4 h ago, following a family dispute, she ingested all of her diabetic father's medications. Her family are unable to account for 75×5 mg glipizide and 29×500 mg metformin tablets. On arrival, she is vomiting and appears anxious and slightly sweaty with a Glasgow Coma Score of 14/15. Her vital signs are pulse rate 90 beats/min, blood pressure 110/75 mm Hg, respiratory rate 18/min, and temperature of 36.8℃. A bedside glucometer reading reveals a blood sugar level (BSL) of 3.0 mmol/l.

RESUSCITATION

The immediate threat to life is hypoglycaemia with the potential for progression to coma and seizures. This patient already exhibits clinical features of mild hypoglycaemia and this is confirmed on bedside testing. Her hypoglycaemia requires immediate correction with establishment of intravenous access and administration of a bolus dose of 50 ml of 50% dextrose solution.

RISK ASSESSMENT

Glipizide is a sulphonylurea oral hypoglycaemic agent. Drugs of this class exert their effect by stimulation of insulin release from the pancreatic beta islet cells. In overdose (of any amount), particularly in non-diabetic patients, they cause prolonged and profound hypoglycaemia. Onset of hypoglycaemia occurs within a few hours of ingestion and, without treatment, progresses in severity. Severe cerebral hypoglycaemia may cause permanent neurological injury or death (box 3).

Metformin is a biguanides. These agents act by increasing cellular insulin sensitivity. Their action is antihyperglycaemic rather than hypoglycaemic and they do not cause severe hypoglycaemic even in overdose. However, overdose of this drug is associated with severe lactic acidosis, a potentially lethal complication. The development of lactic acidosis following metformin overdose does not follow a well defined dose-response relationship and so is difficult to predict. It is thought to be more likely following large overdose or where impairment in renal function slows excretion of the drug (box 3).

In summary, the risk assessment for this particular patient is that, without appropriate management, we expect rapid worsening of her hypoglycaemia with development of severe manifestations of neurohypoglycaemia. The hypoglycaemic effect will be prolonged and profound. Maintenance of euglycaemia by administration of dextrose solutions will be difficult due to rebound hypoglycaemia from further insulin release. In addition, there is a poorly quantifiable risk of metformin induced lactic acidosis, which if not recognised and treated early, poses an additional life threat.

Armed with this individualised risk assessment, we can now plan a rational management plan for our patient.

SUPPORTIVE CARE AND MONITORING

Following initial correction of hypoglycaemia, the patient must be carefully observed for clinical evidence of recurrent hypoglycaemia. This observation includes regular assessment of vital signs and mental status. The observer must be familiar with the neurological and autonomic features of hypoglycaemia and the need to recheck the blood sugar level (BSL) and administer further concentrated dextrose solution should features of hypoglycaemia occur. Any deterioration in the clinical condition of the patient unrelated to hypoglycaemia will act as a prompt to consider the development of lactic acidosis. Regular (at least hourly) estimations of the BSL constitute an integral part of the clinical monitoring.

INVESTIGATIONS

Beyond the routine screening ECG and checking the serum paracetamol level, plus bedside estimations of the BSL, no other investigations are required unless the patient deteriorates clinically. In that case serum electrolytes, creatinine, and lactate would be indicated. Due to the

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Box 1 General approach to acute poisoning

- Resuscitation
  - Airway
  - Breathing
  - Circulation
  - Seizure control
  - Correct hypoglycaemia
  - Correct hyperthermia
  - Resuscitation antidotes
- Risk assessment
- Supportive care and monitoring
- Investigations
  - Screening—ECG, paracetamol
  - Specific
- Decontamination
- Enhanced elimination
- Antidotes
- Disposition

Box 2 Risk assessment: a distinct cognitive step that aims to be quantitative and takes into account:

- 1. Agent(s)
- 2. Dose(s)
- 3. Time since ingestion
- 4. Current clinical status
- 5. Patient factors

Box 3 Sulphonylurea and metformin overdose effects and management

- Sulphonylurea overdose
  - Invariably results in profound and prolonged hypoglycaemia
  - Resuscitation involves correction of hypoglycaemia with IV dextrose
  - Octreotide is the antidote of choice and greatly simplifies subsequent management
- Metformin overdose
  - Usually causes few problems
  - May result in life-threatening lactic acidosis and this complication should be considered in any patient who appears unwell
  - Severe or worsening lactic acidosis mandates urgent haemodialysis

remote location of this patient, these investigations are unavailable prior to transfer.

DECONTAMINATION

The risk-benefit analysis for gastrointestinal decontamination in this patient suggests that it is contraindicated.

Absorption of both of drugs is relatively complete by 1 h and so decontamination at 4 h post-ingestion will have minimal impact on the subsequent clinical course and management.

The risks associated with undertaking this intervention are that rapidly developing hypoglycaemia could produce coma or seizures leading to aspiration of activated charcoal. In addition, performance of the procedure could deflect the attention of medical staff from the more important aspects of patient management. This is particularly important in a small remote hospital with limited staffing.

ENHANCED ELIMINATION

Techniques of enhanced elimination are not useful in the management of sulfonylurea overdose. Urgent haemodialysis is indicated where severe worsening lactic acidosis develops following metformin overdose as it enhances the elimination of metformin and rapidly corrects the profound lactic acidosis.[2–5]

ANTIDOTES

Dextrose is a specific antidote for sulphonylurea poisoning and, as discussed above, is central to resuscitation of the sulphonylurea poisoned patient. However, attempts to maintain euglycaemia by continued infusion of concentrated dextrose is problematic, as administration of glucose stimulates further insulin release and rebound hypoglycaemia[6] and may require administration of excessive volume and osmolar loads. The use of concentrated dextrose solutions to maintain euglycaemia mandates close monitoring in an intensive care or high dependency environment and insertion of a central venous line to avoid phlebitis. In severe cases, euglycaemia may not be achieved even with administrations of large volumes of concentrated dextrose solution. Because of these problems, a number of other pharmacological agents have been employed to maintain euglycaemia and limit dextrose requirements.

Diazoxide acts on the K_{ATP} channels to directly inhibit insulin secretion and has been advocated as a second line antidote.[7 8] However, its use is no longer advocated because of a poor side effect profile that includes orthostatic hypotension, sodium and fluid retention, tachycardia, and excessive catecholamine release.[8 9]

By contrast, octreotide, a synthetic octapeptide analogue of somatostatin, effectively suppresses insulin secretion and has a very benign adverse effect profile.[7] It appears to abolish the need for hypertonic dextrose infusion, thus avoiding the need for a central line, close observation, and complications relating to fluid and electrolyte disturbances. This obviates the need for prolonged ICU admission. Octreotide is now regarded as a first line antidote for sulphonylurea poisoning with the role of dextrose confined to rapid restoration of euglycaemia in the already hypoglycaemic patient and maintenance of euglycaemia until such time as octreotide can be sourced and administered.

Although case reports and series have used doses of 50–100 μg IV or SC q6 hours,[6 10–13] our experience is that such regimes may not completely suppresses insulin release. We recommend a bolus of 50 μg IV followed by an infusion of 25–50 μg/h. Such infusion rates are commonly used for the management of oesophageal varices.[14]

There are no effective antidotes for metformin induced lactic acidosis.

Following initial correction of her low blood sugar level with a bolus dose of 50 ml of 50% dextrose, this patient needs ongoing dextrose administration (for example, 10% dextrose at 100 ml/h titrated to maintain serum glucose at 5–8 mmol/l), whilst availability of octreotide is ascertained. As octreotide represents the definitive management of sulphylurea induced hypoglycaemia, efforts should be made to administer it as soon as possible. If available in the remote area, it can be safely commenced according the administration regime described above. If not immediately available, efforts should be made to move the antidote to the patient as part of the management plan.

DISPOSITION

This patient lives in a remote community with no real inpatient facilities. She needs aerial evacuation with the Royal Flying Doctor Service (RFDS) to a regional hospital with laboratory, medical, and nursing resources and sufficient supplies of octreotide to run an infusion for at least 24 h. She will also need further psychiatric evaluation once the more pressing medical management is underway. This evaluation should commence prior to her being medically cleared.

CLINICAL PROGRESS

Intravenous access is established, the initial hypoglycaemia is corrected with a bolus of 50 ml of 50% dextrose, an infusion of 10% dextrose via a peripheral cannula commenced, and careful monitoring with hourly bedside blood sugars estimations instigated.

It is established that the hospital does not stock octreotide. The RFDS is contacted and asked to evacuate to the regional hospital, some 2 h flying time away. They are asked to take octreotide and further supplies of 50% dextrose with them to the patient. Whilst awaiting transfer to the regional hospital, the patient has another episode of hypoglycaemia with a BSL of 3.0 mmol/l. A further bolus dose of IV 50% dextrose is given and the infusion rate of 10% dextrose increased. On arrival of the RFDS at the remote hospital she is administered a bolus of 50 μg of octreotide prior to being flown to the regional base hospital where an octreotide infusion at 25 μg/h is commenced. Laboratory investigations reveal normal electrolytes and bicarbonate. The dextrose infusion is discontinued and she remains asymptomatic and euglycaemic. The octreotide infusion is ceased at 8 am the following day and continued monitoring of her BSL reveals maintenance of euglycaemia over the subsequent 24 h. She is now medically clear for discharge and arrangements for ongoing management of the social and mental health issues precipitating her self poisoning are well underway. She is safely returned to her community and family a few days later.

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