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Prolonged Bilateral Reactive Miosis as a Symptom of Severe Insulin Intoxication

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Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Conflict of interest: None declared

Patient: Female, 64
Final Diagnosis: Insulin self poisoning
Symptoms: Coma
Medication: —
Clinical Procedure: Supportive care
Specialty: Critical Care Medicine


Objective: Unusual clinical course
Background: Miosis occurs following exposure to toxins that decrease the sympathomimetic tone, increase the cholinergic tone, or exert sedative-hypnotic effects, but has not been reported in insulin poisoning.

Case Report: A 64-year-old woman without co-morbidities was found unconscious next to an empty insulin pen. Her Glasgow Coma Scale was 3 with absent reflexes, bilateral reactive miosis, and injection marks across the abdominal wall. The patient was endotracheally intubated, mechanically ventilated, and transferred to this hospital. At admission, the blood glucose level was 34 mg/dL. Glasgow Coma Scale remained at 3, with persistent bilateral reactive miosis. The toxicology screening was negative for ethanol, barbiturates, tricyclic antidepressants, phenothiazines, amphetamines, cannabinoids, salicylates, acetaminophen, and cocaine. Cranial computed tomography with angiography and magnetic resonance imaging (MRI) did not show any structural brain lesions. Intravenous glucose was continued at 6-14 g/h for 3 days. On repeated neurological examinations, the patient remained deeply comatose, with partial loss of cranial nerve function. Bilateral reactive miosis persisted for 4 days. From day 5 on, the patient awoke progressively. At discharge, the patient was fully alert and orientated, without a focal neurological deficit.

Conclusions: Prolonged bilateral reactive miosis can be a clinical symptom accompanying metabolic encephalopathy in severe insulin poisoning. Functional impairment of the pons due to relative hypoperfusion during hypoglycemia may serve as a reasonable pathophysiologic explanation for this phenomenon.

MeSH Keywords: Brain Diseases, Metabolic • Hypoglycemia • Insulin Coma • Miosis

Full-text PDF: <http://www.amjcaserep.com/abstract/index/idArt/892324>

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Background

Changes in pupillary size are seen in various poisonings and can, together with other symptoms, give important clues regarding the nature of the toxin [1,2]. Dilated pupils (mydriasis) result from intoxication with substances which either increase the sympathomimetic tone (e.g., amphetamines, cocaine) or decrease the cholinergic tone (e.g., antihistamines, antidepressants). Vice versa, pupillary constriction (miosis) occurs following exposure to toxins that decrease the sympathomimetic tone (e.g., clonidine, opioids, neuroleptics), increase the cholinergic tone (e.g., cholinesterase inhibitors, carbachol, muscarine, nicotine), or exert sedative-hypnotic effects (e.g., barbiturates, benzodiazepine, ethanol) [3]. In this case report, we present the clinical course of a patient with severe insulin intoxication who presented with prolonged bilateral reactive miosis. Written informed consent was obtained from the patient for publication of this case report.

Case Report

A 64-year-old Caucasian woman (170 cm, 80 kg) without known co-morbidities or tobacco, alcohol, or substance abuse was found unconscious next to an empty insulin pen (Mixtard®; mixture of fast- and long-acting insulin; maximum filling volume 250 IU) which belonged to her diabetic husband. At the arrival of the emergency team, her Glasgow Coma Scale count was 3. On clinical examination, absent reflexes, bilateral reactive miosis, and multiple injection marks across the abdominal wall were detected. No tablets, blisters packs, or drug containers could be found nearby the patient or anywhere in the apartment. The blood glucose measured with a glucose meter (One Touch Ultra2®; LifeScan Inc, Milpitas, California) was 75 mg/dL, and 33 g of glucose were administered without any changes in the level of consciousness. Injection of naloxon (0.4 mg) and flumazenil (0.5 mg) did not lead to any change in the depressed consciousness level. The patient was then endotracheally intubated for airway protection (fentanyl 0.1 mg; midazolam 5 mg; rocuronium 50 mg), mechanically ventilated, and transferred to this hospital. At admission, the blood glucose level was 34 mg/dL. Glasgow Coma Scale remained at 3, with persistent bilateral reactive miosis. Aside from hypoglycemia, laboratory results were remarkable only for hypokalemia (3.5 mmol/L). The toxicology screening of the urine and blood was negative for ethanol, barbiturates, tricyclic antidepressants, phenothiazines, amphetamines, cannabinoids, salicylates, acetaminophen, and cocaine, but positive for opiates and benzodiazepines, which had both been used for endotracheal intubation. Since the attending emergency and intensive care physicians considered that bilateral reactive miosis was insufficiently explained by insulin poisoning and hypoglycemia, cranial computed tomography with

angiography of the circle of Willis, as well as MRI, were performed to exclude a structural lesion of the brain. Both examinations showed no pathologic results, particularly in the brainstem, including the pons. Cardiopulmonary function was stable with hypertonic arterial blood pressure measurements (systolic blood pressure 150–180 mmHg). After emergent glucose administration, the patient was transferred to the intensive care unit, where the intravenous glucose infusion was continued at 6–14 g/h for 3 days followed by full enteral nutrition to maintain blood glucose levels >80 mg/dL. On repeated neurological examinations, the patient remained deeply comatose, with partial loss of cranial nerve function such as an absent corneal reflex. Electroencephalography showed diffuse, generalized slowing, with maintained reactivity to external stimuli (day 2). Somatosensoric and acoustic evoked potentials were normal (day 4). MRI of the brain repeated on day 4 did neither reveal signs of brain damage. Bilateral reactive miosis persisted for 4 days after admission; on day 5, the pupils changed to mid-size. On days 5 and 6, the patient awoke progressively and was agitated for another 3 days. At intensive care unit discharge (day 11), the patient was fully alert and orientated, without a focal neurological deficit.

Discussion

To the best of our knowledge, this is the first report on prolonged bilateral reactive miosis in a patient with insulin intoxication and metabolic encephalopathy. It may be suspected that this symptom has until now been over-looked or under-reported, thus representing a potential publication bias. Knowledge about the possibility of miosis in insulin poisoning could prevent unnecessary and potentially risky intra-hospital transfers and examinations in an acutely ill, mechanically ventilated patient [4]. Since miosis combined with deep coma and absent reflexes raised the suspicion of concomitant structural lesions of the pons or other brainstem parts, our patient was exposed to the above-mentioned risks.

Co-intoxication with further toxins known to induce miosis was systematically excluded in our patient. In the pre-hospital setting, naloxone and flumazenil were injected without any response, making co-intoxication with either of these substances extremely unlikely. The toxicological analysis of the blood and urine excluded co-intoxication with ethanol, barbiturates, and neuroleptics, all substances that have been associated with miosis [5–7]. Plasma cholinesterase activity measurements were within the normal range and absence of systemic cholinergic symptoms such as salivation, lacrimation, bronchorrhea, gastrointestinal symptoms, and sweating made poisoning with cholinesterase inhibitors, carbachol or muscarine-/nicotine-containing plants/substances equally unlikely.

Whereas mydriasis due to increased sympathetic tone is commonly observed in hypoglycemic subjects, our patient presented with paradoxical miosis. Structural or functional lesions of the pons disrupt descending sympathetic pathways and thus cause bilateral reactive miosis by decreased sympathetic innervations of the pupils. Exclusion of structural lesions of the pons and brainstem by an extensive radiological work-up makes functional impairment of the pons a possible cause of bilateral reactive miosis in our case. Indeed, hypoglycemia-induced relative hypoperfusion of the pons has been reported in 1 physiological study in which Tallroth et al. evaluated cerebral blood flow in 10 regions of the brains of healthy volunteers. Although induction of hypoglycemia was followed by a global increase of cerebral blood flow, this increase was heterogeneous, with the highest increments occurring in the frontal and parietal lobes and the lowest increments found in the pons/brainstem regions [8]. Interestingly, these relative changes in regional cerebral blood flow persisted also after normalization of blood glucose levels [8]. Sontineni et al. reported the case of a diabetic male with basilar artery stenosis who experienced pontine infarction as a complication of hypoglycemia [9]. Insulin-induced hypoglycemia in a patient with insulin-dependent diabetes mellitus resulted in chronic pontine dysfunction [10], confirming the unique vulnerability of the pons to hypoglycemia.

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The remaining clinical presentation of the patient was characteristic for insulin poisoning. Prolonged hypoglycemia requiring high-dose glucose replacement and hypokalemia are well-known features of insulin intoxication. Another noteworthy aspect was the relatively high blood sugar levels in the pre-hospital setting. Since a point-of-care device (a glucose meter) was used and no other causes of coma could retrospectively be identified, we considered this measurement to have been falsely high. False high measurements of blood sugar have repeatedly been reported in hypoglycemic ranges, particularly when measured by point-of-care devices such as a glucose meter [11,12].

Conclusions

Prolonged bilateral reactive miosis can be a clinical symptom accompanying metabolic encephalopathy in severe insulin poisoning. Functional impairment of the pons due to relative hypoperfusion during hypoglycemia may serve as a reasonable pathophysiologic explanation for this phenomenon.

Competing interests

The authors declare that they have no competing interests.