

Minoxidil Toxicity and Febrile Illness in a Pediatric Patient, a Life-Threatening Combination

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Abstract

We are reporting a 10 years old girl, who had a febrile illness in addition to accidental ingestion of minoxidil. This combination led to fast deterioration in her overall condition with severe hypotension, hemodynamic instability and respiratory failure with pulmonary edema requiring high support of vasopressors and ventilation.

The known side effects of minoxidil ingestion was manifested as hypotension, fluid retention, pulmonary edema and refractory shock.

As Minoxidil ingestion is not common among pediatric age group, we are reporting this case highlighting the serious side effects of this medication and the manifestation of minoxidil toxicity.

Keywords: *Minoxidil; Pulmonary Edema; Hypotension; Refractory Shock*

Introduction

Minoxidil, pharmacologically known as 2,4-Diamino-6-piperidinopyrimidine 3-oxide, with this Chemical Formula $C_9H_{15}N_5O$, is basically an arteriolar vasodilator and a potassium channel opener, used in managing hypertension emergencies in addition to wide use as treatment of alopecia and hair loss [1,2].

The drug acts pharmacologically by promoting the vasodilatation by direct arteriolar smooth muscle relaxation. There are multisystem adverse effects reported using minoxidil, including hypotension, sinus tachycardia, pericardial effusion Sodium, and water retention, pulmonary edema, and transient increase in blood urea nitrogen and serum creatinine [1,2].

One of the serious side effects of minoxidil is refractory shock, which has been reported in literature secondary to the ingestion of minoxidil. One case reported a 58 years old gentleman, who presented with refractory shock, papilledema pulmonary edema, and oliguria. He required ICU admission, mechanical ventilation, and inotropic support to control his condition, and he recovered after three days [3].

To the best of our knowledge, refractory shock secondary to minoxidil ingestion has been reported infrequently among both adult and pediatric age group with variable outcome. We are reporting a pediatric patient who develops refractory shock with multi-organ dysfunction secondary to accidental Ingestion of minoxidil.

Case Presentation

This is a ten-year-old girl not known to have chronic diseases before, she was well, till two days prior to her presentation to the hospital when she started to complain of subjective fever and dry cough associated with headache and sore throat. The family managed her at home by oral acetaminophen and ibuprofen.

Subsequently, the patient started to experience worsening in her cough pattern with increasing intensity of her dry cough, the patient accidentally ingests Minoxidil syrup instead of over the counter regular cough syrup as both bottles were stored in the refrigerator next to each other and they look similar. The total amount of ingested minoxidil was 150 mg (3.75 mg/kg).

Few hours post-ingestion, the patient complained of vomiting moderate to large amount seven times of food content yellowish in color in addition to fatigue and dizziness. For that reason, the family presented to our Emergency Department in Qatif Central Hospital, Eastern province, Saudi Arabia 18 hours post-ingestion with the complain of accidental drug ingestion and the manifestation of dizziness and vomiting.

Initial evaluation up on presentation to the emergency room, she was well-looking, conscious, alert, GCS15/15.

Initial vital signs was T 38.0°C, HR 130b/m, RR 22/m, blood pressure 90/65 mmHg and oxygen saturation 99%. reflecting tachycardia and hypotension for age.

The physical examination revealed cold extremities, delayed capillary refill time, and weak peripheral pulses.

Cardiovascular examination revealed normal heart sounds, and no added sounds. Chest auscultation revealed decrease air entry with crepitation over the left lower zone without signs of respiratory distress, Abdomen and neurological examinations were normal. The initial laboratory investigations shown below.

CBC and differential	WBC 5.8 Hemoglobin 10.6 g/dl platelets 301 Neut 55% Lymphocyte 21%
Venous blood gas, RBS and Lactate	PH 7.44 PCO ₂ 34.6 HCO ₃ 24 Lactate 1.4
Serum Electrolytes, Liver function test, Renal function test	Sodium 135 mmol/L Potassium 3.9 mmol/L Creatinine 79 mmol/L Urea 6.9. Albumin 34.1 Calcium 1.97 mmol/L Phosphorus 1.47 mmol/L Magnesium 0.69 mmol/L Total Bilirubin 13.9 mmol/L Direct Bilirubin 5.6 mmol/L ALT 13, AST 19.9
Coagulation profile	PT 17.1 INR 1.35 PTT 37.8

Table 1

Her initial chest X-ray (Figure 1) showed homogenous opacity in the left lower zone.

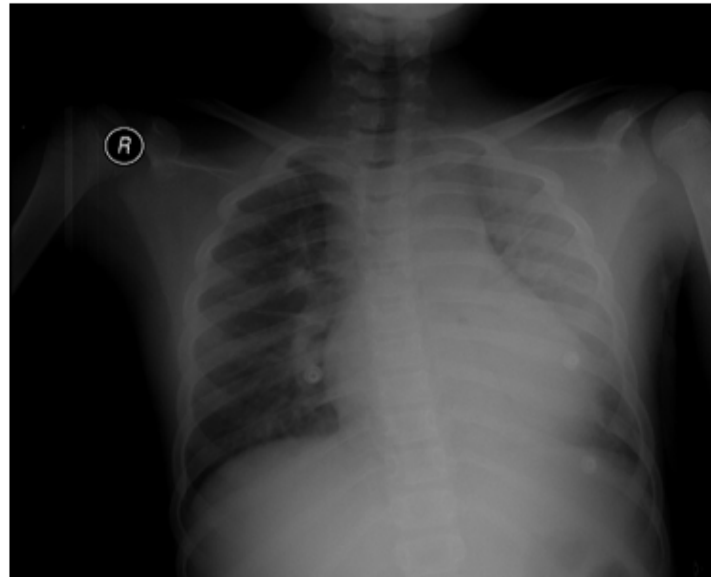


Figure 1

The patient started on empirical antimicrobial therapy, supportive oxygen besides fluid resuscitation started as per PALS guidelines as Normal saline 20 ml/kg. Her blood pressure readings were dropping down, her perfusion was worsening with increased capillary refilling time and cold extremities. Total fluid boluses required was up to 100 ml/kg as her hemodynamics didn't improve in addition to vasopressors. Vasoactive therapy was started by Epinephrine infusion followed by Norepinephrine infusion, Dopamine and Dobutamine were followed as her hemodynamics was declining rapidly to sever hemodynamic instability and sever hypotension, the lowest reading of blood pressure was 36/16 mmhg.

Furthermore, her mental status and respiratory condition start to decline during her hypotension events, she developed respiratory distress with hypoxia (SPO₂ 90%) on a 15 L/min non-rebreather face mask. Her GCS was dropping down 12/15 and her BP was dropping fast, and her perfusion was worsening with cold extremities, delayed capillary refill time to 6seconds. All of the events were simultaneously, and patient overall condition was worsening and crashing down.

For that reason, patient was managed with fluid resuscitation, inotropic support (initiated and gradually maximized to four inotropes), Hydrocortisone, invasive intubation and ventilation, broad spectrum antibiotics. And was admitted to pediatric intensive care unit for further management.

Furthermore, after intubation, the patient started to require higher oxygen requirement and higher ventilator settings. Her respiratory support and conventional mechanical ventilator settings were maximized, but the patient remained hypoxic. Her oxygen saturation was down to 50s and her FiO₂ requirement reached 1. Her OSI reached 17 and the repeated chest X-ray (Figure 2) showed bilateral infiltrates. Based on these findings, respiratory support escalated to high-frequency Oscillatory ventilation HFOV with FiO₂ requirement up to 1.

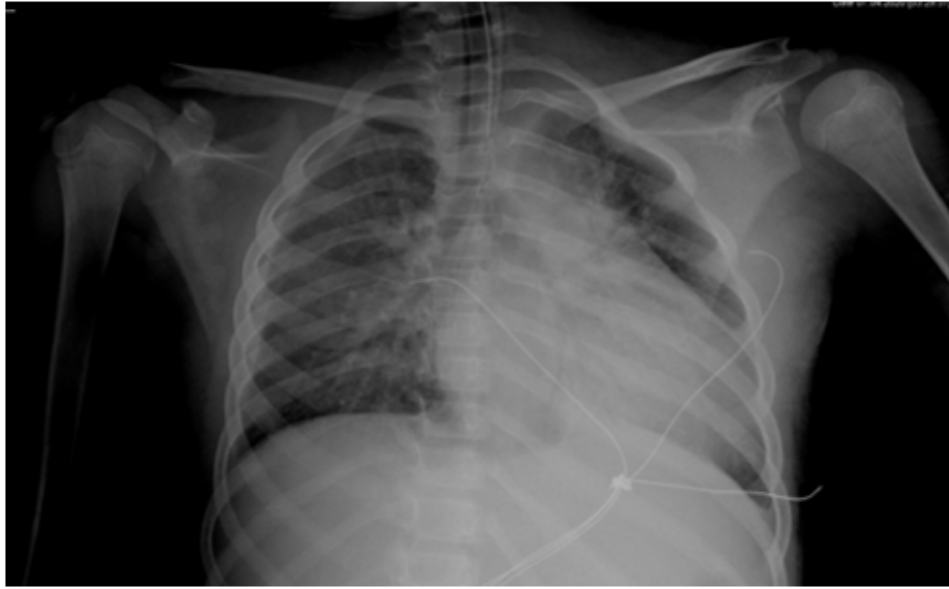


Figure 2

Formulating a problem list to the patient clinical manifestation, our initial impression was the following:

1. Minoxidil intoxication with refractory shock and severe hemodynamic instability.
2. Acute hypoxic hypercapnic respiratory failure 2ry to bronchopneumonia to rule out COVID-19.
3. Severe ARDS (OSI 17).
4. Acute kidney injury.

Echocardiography done to evaluate the cardiac function, showed normal heart structure and function, no evidence of pulmonary hypertension, and no pericardial effusion.

By day two of admission to pediatric intensive care unit, the patient critically sick, worsening AKI and climbing up creatinine trends with declining of her urine output. She was receiving maximum medical support and she remained contentiously febrile, high grade temperature and partially responding to acetaminophen.

Multidisciplinary team involved including (Pediatric infectious diseases, pediatric hematology, pediatric nephrology, pediatric rheumatology as well).

Further management plan was including initiation of COVID19 treatment empirically before the result of the nasopharyngeal swab as the disease is spreading and reaching pandemic definition. Patient received IVIG and steroid therapy.

In addition to that, we proceed with empirical plasma exchange as well hoping to decrease viral load and to washout toxins.

Management received was sedation infusion, muscle relaxant infusion, ventilation and oxygenation with HFOV, broad spectrum IV antibiotics, antiviral therapy, COVID19 directed therapy as per Saudi Arabia MOH protocol version 1.1 March 19th, 2020, blood products, plasma exchange, diuretics.

In the following day, the respiratory status of the patient showed improvement and started on gradual weaning of respiratory support, her chest x-ray was improving as well, and by the end of day five of admission, all inotropic support discontinued after gradual weaning and restoration to good circulation and end organ perfusion.

After a week of admission, by day eight, the patient was successfully extubated, and her neurological examination was normal apart from mild proximal muscle weakness, which is consistent with critical illness myopathy.

The patient started on physical rehabilitation and showed regain of her muscle tones and power.

Laboratory

Blood, urine, tracheal aspirate cultures and PCR for SARS-CoV2 virus, in addition to a nasopharyngeal swab of the respiratory viral panel (include 23 respiratory viruses) all came negative.

Discussion

Minoxidil act through different mechanisms in human body. It works as a direct arteriolar vasodilator with no effect on venous vessels, blocking calcium channel, and stimulant to the renin-angiotensin-aldosterone system. These mechanisms will result in a fall in peripheral vascular resistance and hence decrease blood pressure. On the other hand, these processes will result in reflex stimulation of sympathetic and renin-angiotensin-aldosterone systems and hence induce tachycardia in addition to sodium and water retention [1,2].

These physiological effects can explain the profound hypotension in addition to tachycardia and pulmonary edema in the case of minoxidil toxicity. For that reason, minoxidil used in combination with beta-blockers and loop diuretics in management of refractory hypertensive emergencies to prevent tachycardia and sodium-water retention while preserving the hypotensive effect of minoxidil [1,2].

Our patient showed similar pathophysiological consequences. She was presented to our hospital with tachycardia and hypotension, secondary to accidental ingestion of topical minoxidil with underlying pneumonia. She was refractory to fluid management require initiation of inotropic support, develop pulmonary edema secondary to fluid resuscitation. Her shock state stabilized by 24 hours from admission and weaned off from inotropes after 5 days.

Our patient shares a similar clinical course to other patient reported in the literature both from adult and pediatric age groups. Isabelle Caludet, *et al.* [4] in 2015, reported a 7-year-old boy who presented 7 hours post ingestion of 250 mg of minoxidil, he was tachycardic hypotensive, treated with fluid only, no inotropic support initiated, he remained hypotensive and tachycardic for total 40 hours until full recovery. Another care reported by Aprahamian, *et al.* [5] in 2011 of young girl presented with similar picture after ingestion of 100 mg of minoxidil and her overall condition improve by 36 hours.

T.P. Shashikala, *et al.* [3] reported a 58-year-old male patient who accidentally ingest topical minoxidil, then he presented 12 hours later with complain of vomiting and found to be hypotensive and tachycardic. He was refractory to fluid management and required dopamine infusion norepinephrine and vasopressin, his course complicated by hypoxic respiratory failure secondary to pulmonary edema. His overall condition stabilized after 12 hours of management and tolerated weaning from ventilation and vasopressors. Alexander Gar-rad, *et al.* [6] reported 48 year old male who presented in refractory hypotension after ingestion of minoxidil, He required dopamine and norepinephrine in addition to phenylephrine and midodrine, his overall all condition improved after 30 hours post ingestion.

Conclusion

A small amount of minoxidil ingestion has a catastrophic cardiovascular compromise in children as well as adults causing severe hypotension, refractory shock and life threatening consequences of multiorgan involvements.

As Minoxidil is widely used recently widely used as topical and oral medication for hair growth, this product must be preserved in a child resistant container out of reach from children to prevent such serious events from accidental ingestions. Consumer of this product for its dermatological effect must be aware about the serious side effect of minoxidil on children.

Consent

Written consent was taken from the parents for approval of case reporting and publishing.

Acknowledgment

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Conflicts of Interest

None.

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Contribution of Authors

Preparation of first draft: I.M, F.B, Z.R.

Literature review: Z.R, F.B, I.M.

Conceptualization: F.B, I.M.

Intellectual inputs for improvement of I.M, F.B.

Approval of final draft: I.M, F.B.

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