Case Report

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Accidental Consumption of Distinguished Substance in Disguise- A Rare Case of Minoxidil Poisoning

Internal Medicine Section

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ABSTRACT

Minoxidil is a powerful direct acting vasodilator that was used clinically as an oral antihypertensive drug in combination with beta blockers and diuretics in cases of hypertension refractory to other antihypertensives. A 58-year-old male presented to the Emergency Department with an alleged history of accidental consumption of around 10 mL of 5% topical minoxidil solution. He had developed tachycardia, severe hypotension, and characteristic Electrocardiogram (ECG) changes with no obvious chest pain. He was treated with continuous intravenous (i.v.) crystalloids, dual inotropes and other supportive measures. The patient also developed acute pulmonary oedema and acute kidney injury. He responded to treatment and gradually improved haemodynamically with resolution of ECG changes and acute kidney injury. He was discharged seven days after admission. The patient showed resolution of characteristic ECG changes and improvement in haemodynamic condition of patient with supportive management in hospital.

Keywords: Arrhythmias, Haemodynamic instability, Toxicity

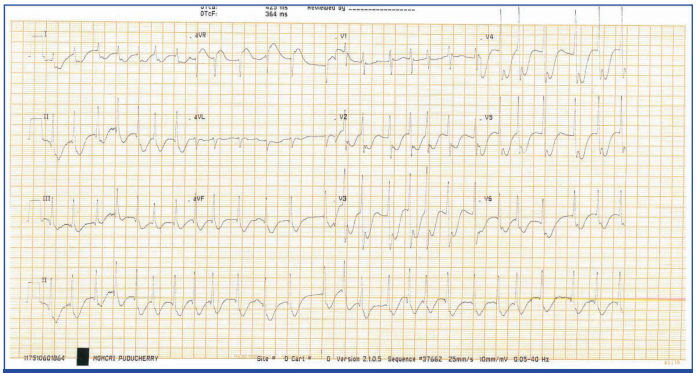
CASE REPORT

A 58-year-old male patient presented to Emergency Medical Services (EMS) Department of a tertiary care hospital at 11:00 pm with an alleged history of accidental consumption of around 10 mL of 5% topical minoxidil solution. The patient had minoxidil drug sample bottles at his residence as his son was a medical representative and those sample bottles were stored in old alcohol bottles for discarding purpose. Patient consumed the drug mistakenly thinking it as an alcohol at 7pm on the day of reporting for hospital. The patient developed giddiness and two episodes of vomiting without chest pain or breathlessness following consumption. Patient was initially taken to local clinic where they found the patient had severe hypotension and was started on dual inotropic support, and referred to tertiary care hospital for further management.

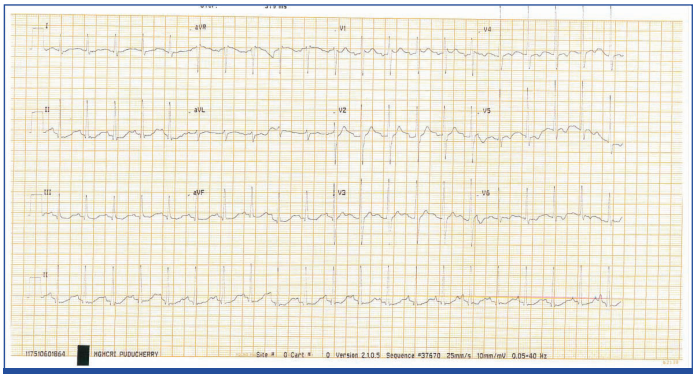
On presentation, the patient was conscious, restless, afebrile with vital signs as pulse 170 beats/min, blood pressure of 50/20 mmHg, respiratory rate of 30 respiration/min. In view of haemodynamic instability, he was given a fluid challenge with intravenous crystalloids and dual inotropes. Later, intravenous (i.v.) fluids were eventually stopped and the patient was kept on continuous inotrope support. Gastric lavage was performed.

Electrocardiogram (ECG) revealed atrial fibrillation with rapid ventricular rate with incomplete Right Bundle Branch Block (RBBB) pattern [Table/Fig-1]. He had revealed elevated total White Blood Cells (WBC) counts 26,700 cells/mm^3, creatinine 1.40 mg/dL, low serum potassium 3.0 mEq/L and normal cardiac enzymes {Creatine phosphokinase-N-acetyl-cystein (CPK-NAC):182U/L, Creatine phosphokinase-MB (CPK-MB):32U/L, Troponin I was negative}. Arterial blood gas analysis showed hypoxia and metabolic acidosis (pH: 7.25, pCO_2:38, pO_2:61, HCO_3:16, SpO_2:87%, anion gap: 9.0 mEq/L).

Patient was started on prophylactic antibiotics (Inj.ceftriaxone 1 gm) in view of elevated total counts after sending blood, urine and sputum cultures. Continuous cardiac monitoring was done for two days. Inotropes were titrated according to Mean Arterial Pressure (MAP) (target MAP of 65 mmHg), then gradually tapered and stopped. Serial ECG monitoring done on day 2 [Table/Fig-2] was found to have gradual control in heart rate and stabilisation of ECG. [Table/Fig-3] showed laboratory parameters and the trend



[Table/Fig-1]: (Day 1 ECG)- A-Fib with RVR and incomplete RBBB pattern.
A-Fib: Atrial fibrillation; RVR: Rapid ventricular response; RBBB: Right bundle branch block; ECG: Electrocardiogram



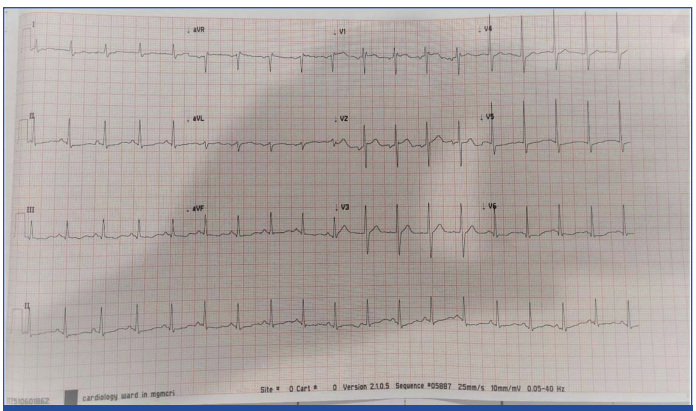
[Table/Fig-2]: (Day 2 ECG)-Gradual resolution of A-Fib and incomplete RBBB pattern.
ECG: Electrocardiogram

of biochemical and haematological parameters during seven days of hospital stay. Total counts gradually came to normal levels after initiation of antibiotics. Renal parameters gradually became normal without any requirement of haemodialysis. Serial measurement of cardiac enzymes repeated after 6 hours (Trop-I:570 ng/L) and 12 hours (Trop-I:178 ng/L) showed a decreasing trend. During hospital stay, patient was found to have high fasting blood sugar (280 mg/dL) and HbA1C (12.2 g%). The patient was thus initiated with split dose insulin, and careful monitoring of blood glucose levels and insulin dose titrated accordingly.

S. No.	Lab test	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6
1.	Total counts (cells/mm^3)	26700	22200	15600	13400	10900	11500
2.	Haemoglobin (gm/dL)	11.3	12.6	11.2	11.0	11.4	13.3
3.	Platelet count (cells/mm^3)	348000	387000	293000	253000	285000	436000
4.	Blood urea (mg/dL)	26	31	49	59	55	-
5.	Creatinine (mg/dL)	1.40	1.25	0.99	0.93	0.84	-
6.	Sodium (mEq/L)	139	142	144	140	139	-
7.	Potassium (mEq/L)	3.0	2.9	3.7	3.5	4.1	-
8.	Chloride (mEq/L)	114	112	115	109	106	-
9.	Calcium (mg/dL)	7.9	-	7.5	-	-	-
10.	Magnesium (mg/dL)	2.4	-	-	-	-	-
11.	Phosphorous (mg/dL)	3.9	-	-	-	-	-
12.	Total protein (gm/dL)	5.8	6.1	-	5.3	-	-
13.	Albumin (gm/dL)	3.5	3.7	-	3.1	-	-
14.	Total bilirubin (mg/dL)	0.4	0.5	-	0.8	-	-
15.	Direct bilirubin (mg/dL)	0.2	0.2	-	0.2	-	-
16.	SGOT (U/L)	34	25	-	26	-	-
17.	SGPT (U/L)	26	21	-	23	-	-
18.	ALT (U/L)	91	81	-	72	-	-
19.	CRP	Negative	-	-	-	-	-
20.	ESR (mm/hr)	40	-	-	-	-	-
21.	Ferritin (ng/mL)	47.5	-	-	-	-	-
22.	D dimer (ng/mL)	568	-	-	-	-	-
23.	Urine Routine	Bacteria-nil	-	-	-	-	-
24.	CPK-NAC (U/L)	182	294	216	-	-	-
25.	CPK-MB (U/L)	32	20	12	-	-	-
26.	Trop-I (ng/L)	Negative	570	178	-	-	-
27.	PT-INR (sec)	0.89	-	-	-	-	-
28.	APTT (sec)	31.8	-	-	-	-	-
29.	ABG (mmHg), HCO3 (mEq/L)	pH: 7.25, pCO_2:38, pO_2:61, HCO_3:16, SO_2:87	pH: 7.31, pCO_2:34, pO_2:60, HCO_3:17, SO_2:88	pH: 7.36, pCO_2:35, pO_2:74, HCO_3:19, SO_2:94	pH: 7.46, pCO_2:31, pO_2:66, HCO_3:22, SO_2:94	pH: 7.47, pCO_2:33, pO_2:62, HCO_3:24, SO_2:93	pH: 7.43, pCO_2:38, pO_2:86, HCO_3:25, SO_2:97
30.	Cultures	**1) Urine culture:** Sterile **2) Blood culture:** Sterile **3) Sputum culture:** *Klebsiella Pneumonia*-ESBL producer	-	-	-	-	

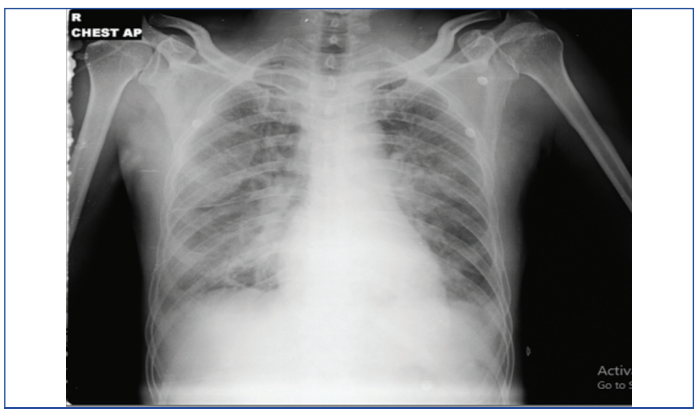
[Table/Fig-3]: Laboratory parameters during hospital stay of one week.
SGOT: Serum glutamic-oxalacetic transaminase; SGPT: Serum glutamic-pyruvic transaminase; ALT: Alanine aminotransferase; CRP: C-reactive protein test; ESR: Erythrocyte sedimentation rate; PT/INR: Prothrombin time and international normalised ratio; APTT: Activated partial thromboplastin time; ABG: Arterial blood gases; CPK-NAC: Creatine phosphokinase-N-acetyl-cystein; CPK-MB: Creatine phosphokinase -MB; Troponin- I

During the hospital stay on day 3, patient had breathlessness, tachypnoea, sudden desaturation (SpO_2 -84%) and auscultation of the chest revealed crepitations. ECG on day 3 [Table/Fig-4] found to have normal sinus rhythm with no QRS abnormality and resolving early changes.



[Table/Fig-4]: [DAY 3 ECG] - Controlled rate with resolution of earlier changes.

Chest X-ray Anteroposterior view [Table/Fig-5] showed acute pulmonary oedema and was started on NIV with low dose diuretics (Injection furosemide 10-20 mg intravenously). Then gradually NIV support was weaned off and he was kept on room air by the



[Table/Fig-5]: [Day 3 x-ray chest anteroposterior view]- features of acute pulmonary oedema.

next day. On day 3, the patient showed gradual improvement in his clinical condition with normalising blood pressure (120/70 mm Hg). He was given antibiotics (injection ceftriaxone 1 gm i.v.), low dose diuretics (injection furosemide 20 mg i.v.), proton pump inhibitors (injection pantoprazole 40 mg i.v.) and other supportive medications. Chest physiotherapy and incentive spirometry were given periodically along with antibiotic coverage. Sputum culture showed *Klebsiella pneumoniae*-extended-spectrum β-lactamases (ESBL) producer. Blood and urine cultures found to be sterile. Antibiotics continued according to sensitivity pattern. The patient was eventually discharged after seven days of hospital stay with normal haemodynamic condition.

DISCUSSION

Minoxidil is a powerful direct acting vasodilator that was used clinically as an oral antihypertensive drug in combination with beta blockers and diuretics in cases of hypertension refractory to other antihypertensives [1]. Exact mechanism of action of Minoxidil is not clear. Minoxidil is used topically to treat androgenic alopecia of the scalp (2%, 5% minoxidil solutions) due to its hair growth stimulatory effect [2]. Minoxidil, when taken orally, may result in severe hypotension by direct arteriolar vasodilation, reflex tachycardia or reflux increase in cardiac output and myocardial contractility mediated by the sympathetic nervous system and it results in dynamic ECG changes, acute coronary syndrome, acute kidney injury [3-5]. Immediate resuscitation of the patient is mandatory to improve the haemodynamic status and to reverse other dynamic changes that occurred.

Minoxidil, which was originally used for the treatment of hypertension, recently has been approved for the treatment of male pattern baldness [6]. Adverse effects of local application of minoxidil on scalp are rare and minor. Most commonly it can cause itching and irritation on the affected area with other dermatological complications and minor systemic effects due to its small resorption. The systemic administration of minoxidil is associated with more serious complications.

Minoxidil is activated in the liver and its action is to relax vascular smooth muscle by opening cell surface potassium channels causing an efflux of potassium, hyperpolarisation and relaxation of smooth muscle cells [7]. Minoxidil produces systemic hypotension by direct arteriolar vasodilatation [8]. It is associated with a reflex increase in cardiac output and myocardial contractility mediated by the sympathetic nervous system [9]. Maximal concentration in the blood is achieved 1 hour after oral administration, but due to delay of active metabolic formation, the maximal therapeutic effect appears much later [10].

At least 95% of orally administered minoxidil is absorbed from the gastrointestinal tract and is metabolised to the direct acting vasodilator minoxidil-N-O-sulphate and the less pharmacologically active minoxidil-O-glucuronide [11]. Minoxidil sulphate activates the Adenosine triphosphate (ATP)-modulated K^+ channel. By opening K^+ channels in smooth muscle and thereby permitting K^+ efflux, it causes hyperpolarisation and relaxation of smooth muscle [12]. Like hydralazine, minoxidil dilates arterioles but not veins.

Maximal hypotensive effects may be delayed due to the delay in the formation of the active metabolite. Minoxidil has a plasma half life of 3-4 hour, but its duration of action is 24 hour or occasionally even longer. It has been proposed that the persistence of minoxidil in vascular smooth muscle is responsible for this discrepancy.

Petkosva L et al., showed that minoxidil if ingested orally lead to severe hypotension, acute coronary syndrome, compensatory tachycardia, subendocardial ischaemia and acute kidney failure. In the above study, first day ECG showed diffusely inverted T waves with depressed ST segments in v_2-v_6 and laboratory findings were leucocytosis, elevated CPK-NAC, CPK-MB and increased renal parameters. ECG changes completely resolved by third day and lab parameters were gradually returned to normal by tenth day [12]. Exactly similar clinical, ECG and lab findings have been noticed in the present case where ECG and lab abnormalities resolved in similar fashion.

The cardiac consequences of the baroreceptor-mediated activation of the sympathetic nervous system during minoxidil therapy are an increase in heart rate, myocardial contractility and myocardial O_2 consumption [13]. Thus, myocardial ischaemia can be induced by minoxidil in patients with coronary artery disease [14]. Panchal SK et al., reported a case of minoxidil exposure (3000 mg). The features were severe hypotension, tachycardia, subendocardial ischaemia which were treated efficiently with combination of crystalloids and norepinephrine where patient responded immediately. Initial ECG changes reverted to normal within 1 day. The subendocardial ischaemia was believed to be caused by increased myocardial oxygen demand and decreased coronary perfusion pressure secondary to extreme hypotension and tachycardia and immediate initiation of norepinephrine instead of dopamine have minimised myocardial ischaemia [5]. Contrarily, in the present case, it took 3 days for complete resolution of ECG changes despite of dual inotrope usage.

Various cardiovascular manifestations were noted with different doses of minoxidil in earlier studies [9,12,15,16]. Low doses may produce hypotension and successive increase in doses results in tachycardia and myocardial ischaemia, which may be probably a compensatory mechanism for severe hypotension [7,16]. In this patient, there was tachycardia, severe hypotension and characteristic ECG changes similar to typical ECG changes mentioned in earlier studies [5,9,15]. The measurement of serum levels of minoxidil would strengthen our report, but minoxidil is not detectable in the routinely performed toxic screen analysis in our country [12].

Forrester MB studied 125 cases of minoxidil exposures that were reported to Texas Poison centres during 2000-2014, and found that most exposures involved were due to ingestion (92%), were unintentional (98%) and involved patients who were of age 1-2 years of age. This study showed most of patients were managed on site (62%) i.e., at home and with incidence of minimal adverse effects like vomiting [8].

Even though above study states that exposure to minoxidil causes mild symptoms perse in majority of children, adult population who were using it must be cautious and must keep minoxidil outreach to children and alcoholic addicts as few case reports showed severe cardiac manifestations due to minoxidil exposure [4,17].

CONCLUSION(S)

Accidental ingestion of topical minoxidil showed tachycardia, severe hypotension and characteristic ECG changes. Immediate resuscitation of a patient with fluid challenge and inotropes had a role in control of haemodynamic status over 2 days and to reverse other characteristic changes occurred in ECG occurred. Minoxidil, which is available for topical use, must be kept in a safe place by the user as it is equally dangerous for children and alcoholics, if ingested. The present case was one of clear cut example where it showed improper storage lead to accidental consumption of the substance in thought of it as an alcohol.

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