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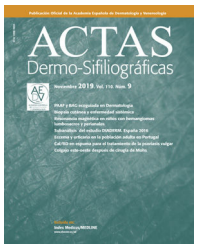

CASE AND RESEARCH LETTER

Serious Adverse effects From Compounding Errors With Low-Dose Oral Minoxidil for Alopecia Treatment

''Efectos adversos graves por errores de formulación de minoxidil oral a bajas dosis para el tratamiento de la alopecia''

To the Editor,

Low doses of oral minoxidil (LDOM) (0.5–1 mg daily in women and 2.5–5 mg daily in men) is an emergent off-label therapeutic approach that have shown to be effective for the treatment of various hair disorders such as androgenetic alopecia (AGA)[1,2] or lichen planopilaris.[3] While doses between 1.25 and 5 mg can be obtained by halving or quartering the marketed drug (Loniten®, Pfizer), doses below 1 mg require to be compounded in the pharmacy in most countries. The main advantage of the oral formulation is the greater adherence of the patient as topical minoxidil is tedious to apply. Based on the published studies, the safety profile of LDOM for hair loss seems to be excellent,[2,4,5] with a low rate of systemic adverse effects and less than 3% of patients requiring discontinuation of the drug.[4] Nevertheless, the aim of this communication is to report a case series of 12 patients that developed serious adverse effects with LDOM.

We performed a retrospective multicentric review between January 2018 and October 2020 including 12 women (mean age 46.5 years, range 25–73) receiving LDOM for AGA who developed serious adverse effects (Table 1). Approximately 1700 prescriptions of the drug were indicated in that period of time and therefore, serious adverse events accounted for 0.7%. The prescribed dose of oral minoxidil ranged between 0.5 and 1 mg as a formulated compound in capsules. The observed systemic adverse effects included hypotensive syncope ($n = 6$), generalized edema ($n = 6$), stroke ($n = 1$) and myocardial infarction ($n = 1$). After a pharmacological analysis of the formulated capsules by an external laboratory, all the patients were receiving doses higher than prescribed due to a compounding mistake (real dose ranging between 50 and 1000 mg per capsule).

Interestingly, none of the women had any previous cardiological condition or were treated for hypertension. In the majority of patients (84.6%), the adverse effects appeared promptly after the first intake and in the rest, during the first week of treatment. In all but two patients the formulated dose was between 10 and 100 times the prescribed dose and was associated with reflex tachycardia, headache, generalized edema and episodes of hypotensive pre or syncope. In the patient who suffered an ischemic stroke, it was determined that the dose formulated by the pharmacist was a thousand times higher than the medical prescription. In the case of the patient who suffered a myocardial infarction, it was determined that the dose increase could have reached 200 times the prescribed dose. All the patients experienced a full recovery of their respective adverse effects. In four patients (33%), LDOM was restarted at the correct dose without any systemic adverse effect. It was concluded that all severe systemic adverse effects reviewed were dose-dependent and not idiosyncratic as they generally appeared after the first dose; they shared the same pathophysiology (severe vasodilation); the drug capsules were formulated by a pharmacist and dosage error was found in every patient and; the most severe effects occurred at higher doses.

In conclusion, we report a case series of patients with AGA suffering serious adverse effects due to compounding errors of LDOM. Given the increase off-label use of LDOM by dermatologists for the treatment of hair disorders, these data are especially relevant for two reasons. Firstly, every severe adverse effect appeared with doses significantly higher (at least 10 times) than the described LDOM. Secondly, in countries where marketed oral minoxidil is not available at low dose (e.g. Loniten® 2.5 mg) and therefore oral minoxidil is formulated by a pharmacist per medical prescription, the pharmacist should know the doses of oral minoxidil used for hair loss and should take care in order to correctly compound the drug.

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Table 1 Clinical and epidemiological characteristics of the 12 women with androgenetic alopecia who developed serious adverse effects with oral minoxidil due to compounding errors.

#	Age (years)	Weight (kg)	Dose prescribed by dermatologist (daily)	Dose formulated by pharmacist	Adverse effect	Onset	Minoxidil reintroduced
1	56	62	0.5 mg	54 mg	Hypotensive syncope, cranioencephalic traumatism and generalized edema.	First intake	No
2	28	60	0.5 mg	48 mg	Hypotensive pre-syncope, headache, and tachycardia.	First intake	Yes
3	32	56	0.5 mg	50 mg	Hypotensive syncope, headache, and tachycardia.	First intake	Yes
4	42	68	0.5 mg	20–100 times the prescribed dose	Hypotensive syncope, headache, tachycardia, and generalized edema.	Second intake	No
5	73	80	0.5 mg	20–100 times the prescribed dose	Hypotensive syncope, headache, tachycardia, and generalized edema.	Third intake	No
6	65	Unknown	1 mg	1000 mg	Hypotensive syncope, ischemic stroke.	First intake	No
7	37	Unknown	1 mg	20–100 times the prescribed dose	Headache, tachycardia, angina, troponin elevation.	First intake	No
8	25	55	1 mg	20–100 times the prescribed dose	Headache and tachycardia	First intake	Yes
9	44	60	0.75 mg	20–100 times the prescribed dose	Headache, tachycardia, and generalized edema.	First intake	No
10	60	Unknown	0.5 mg	20–100 times the prescribed dose	Hypotensive syncope, headache, tachycardia, and generalized edema.	First intake	No
11	45	Unknown	0.5 mg	50 mg	Generalized edema.	First week	Yes
12	52	Unknown	0.5 mg	50–200 times the prescribed dose	Headache, tachycardia, angina, troponin elevation, Non-ST-elevation myocardial infarction.	First intake	No

Conflict of interest

The authors declare that they have no conflict of interest.

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