

histologic pattern shows a lymphocytic infiltrate, sometimes mimicking cutaneous lymphoma; thus, this syndrome is also called drug-induced pseudolymphoma. The diagnosis of the hypersensitivity syndrome is usually slow due to its late onset (3–6 weeks after the beginning of the treatment with the drug), and its slow, potentially fatal evolution. The mortality rate is about 10%. The drugs frequently involved are aromatic antiepileptic drugs (phenytoin, carbamazepine, and phenobarbital), and also allopurinol, gold salts, diapasone, and sorbinil. Up to now, isoniazid has not been described as causing this syndrome. Recovery is usually complete except for the rash, and hepatitis can persist for several weeks. The culprit drug has to be stopped, and corticosteroid treatment is often given at the acute stage. The treatment with steroids has been shown to be effective (2), although the use of this treatment is not completely accepted, especially for patients with allopurinol-induced hypersensitivity syndrome. Some patients have relapses even without reintroduction, mostly during corticosteroid decrease (3).

The hypersensitivity syndrome seems to be an idiosyncratic reaction; individual differences in the metabolism of aromatic anticonvulsants or sulfonamides may predispose patients to such reactions. Some cross-reactions have been observed between the different anticonvulsant drugs.

This syndrome represents only a severe form of hypersensitivity reaction. It is necessary to change this term to decrease the ambiguity of this denomination.

Cutaneous eruptions from isoniazid have been described in less than 1% of the patients treated. Cases of contact dermatitis have also been described in nurses and workers in the pharmaceutical industry (4, 5).

The patch test has been shown to be effective in the diagnosis of contact eczema and also in some cases of reactions to drugs (carbamazepine, tetrazepam, practolol, and pyrazolines) (6). In the case of hypersensitivity syndrome due to antiepileptic drugs, several

cases with a positive patch test to carbamazepine have been reported (7).

The case that we report clinically is presented as hypersensitivity syndrome, but the drug involved, as confirmed by the epicutaneous tests, was isoniazid.

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Mixing albuterol and corticosteroid is not additive

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Key words: ADRR; aerosol therapy; albuterol; beclomethasone; flunisolide; PDRR.

● NEBULIZERS are still frequently used to treat patients with obstructive syndromes. β_2 -Agonists or corticosteroids are commonly used, frequently together. The best method of measuring nebulizer output is “direct drug

assay”, particularly, percentage of drug within the respirable range

(particle size of 1–5 μ m) (1, 2).

It is known that any alteration in the physicochemical characteristics

of a nebulizing solution may produce unexpected results in the amount of drug available to patients (3). Therefore, when drugs are nebulized together, there could be a variation in the output of each single drug.

We have studied the amount of albuterol (Alb), flunisolide (Flu), and beclomethasone dipropionate (BDP) within respirable range (ADRR) when nebulized separately or in a mixture of Alb and corticosteroid.

We employed Mobyneb Aerosol Systems (MEFAR, Bovezzo, Brescia, Italy). This “active Venturi” nebulizer is more efficient than conventional jet nebulizers (4). The volume fill used was 0.8 ml of Alb (Broncovaleas sol. 5 mg/ml, Valeas, Milan, Italy) in 4 ml of saline solution (1 mg/ml) and BDP 400 μ g/ml (Clenil A f., 400 μ g/ml, Chiesi, Parma, Italy). In each case, nebulization was repeated at 1, 2, and 3 min, and each test was repeated six times.

Concentrations of the tested drugs were determined in duplicate by HPLC, by peak area ratio comparison with standard curves, linear over a range of interest. Standard solutions were made up in drug-free phosphate buffer with concentrations ranging from 0.1 to 50 mg/l. The HPLC system consisted of a Shimadzu liquid chromatograph equipped with a variable-wavelength UV detector (SPD 6 A), a fluorescence detector (Waters 470), LC-9A pumps, an autosampler (SIL 9A), and a reverse phase column C18 Spherisorb.

For Alb, the flow rate was 1.1 ml min⁻¹. The effluent was monitored at an excitation wavelength of 276 nm with emission set at 609 nm. The limit of quantitation was estimated to be 50 μ g/l. Inter- and intra-assay coefficients of variation were 5.1 and 6.0, respectively.

The availability of β_2 -agonist or corticosteroid is lower in drugs nebulized together.

Table 1. ADRR at different times

Drugs nebulized alone				
	1 min	2 min	3 min	
Albuterol	1 mg/ml	441	783	1050
Flunisolide	0.5 mg/ml	279	407	559
Beclomethasone	0.13 mg/ml	85	154	265
Albuterol and flunisolide nebulized together				
	1 min	2 min	3 min	
Albuterol	1 mg/ml	368 (17)	594 (24)	951 (10)
Flunisolide	0.5 mg/ml	139 (50)	235 (42)	384 (31)
Albuterol and beclomethasone nebulized together				
	1 min	2 min	3 min	
Albuterol	1 mg/ml	340 (23)	676 (14)	1044 (1)
Beclomethasone	0.13 mg/ml	55 (35)	112 (27)	169 (36)

Number in parentheses represents percentage of drug reduction when two drugs were nebulized together.

For BDP, the effluent was monitored with the UV detector (254 nm). The limit of quantitation was estimated to be 5 mg/l. Inter- and intra-assay coefficients of variation were 5.7 and 6.4, respectively.

For Flu, the flow rate was 1 ml min⁻¹. The effluent was monitored with the UV detector (264 nm). The limit of quantitation was estimated to be 5 mg/l. Inter- and intra-assay coefficients of variation were 5.2 and 6.5, respectively.

A laser diffraction analyzer (API aerosizer®) was used to determine the aerosol particle-size distribution. Percent output within the respirable range (PORR) (5), i.e., the fraction of aerosol capable of entering and remaining in the lung, was calculated after 1, 2, and 3 min of nebulization. The particle-size distribution was used to calculate the respirable fraction as the fraction of the volume of aerosol contained in particles of 1–5 µm in diameter (6).

For evaluation of the ADRR (µg/min) available to the patient, the following calculation was made: mean per minute of drug output multiplied by PORR. The standard

deviation of the ADRR value proved to be low, ranging from 5.7 to 6.5% in the solutions and from 5.2 to 12.6% in the suspension.

Table 1 shows the ADRR at different times. The reductions were evident (in parentheses) when the drugs were administered together. This reduction was more evident (Student's *t*-test, *P* < 0.05) in the corticosteroids than in Alb.

From these data, we can assume that the best sequence of aerosol therapy for patients suffering from obstructive syndromes would be, first, Alb to reduce bronchial obstruction, followed by corticosteroid to reduce the inflammation. Should drugs be used together, their concentration must be adjusted to compensate for the observed reduction in ADRR.

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