

Acute pulmonary reaction to nitrofurantoin

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Pinerua, R. F. and Hartnett, B. J. S. (1974). *Thorax*, 29, 599–602. **Acute pulmonary reaction to nitrofurantoin.** Acute pulmonary reaction to nitrofurantoin is a rare complication of a commonly used drug. This report of such a reaction presents studies of pulmonary function more detailed than are so far available. Studies made nine days after the drug had been withdrawn showed arterial hypoxaemia and abnormalities in ventilation-perfusion relationships. Challenge with 200 mg nitrofurantoin produced increased minute ventilation, hypoxaemia, hypocapnia, deterioration in ventilation-perfusion relationships, marked veno-arterial shunting, and a fall in steady-state transfer factor for carbon monoxide and fractional carbon monoxide uptake. Spirometry and lung volume measurements indicated a restrictive lung abnormality without effect on large airways which persisted for at least nine weeks. Three years later there had been complete resolution of the process, apart from some persistent reduction in transfer factor, possibly related to the patient's smoking habits.

The clinical manifestations of acute pulmonary hypersensitivity to nitrofurantoin have been documented since recognition of this syndrome by Israel and Diamond (1962) and the earlier observations by Rebhun (1956) and Fisk (1957) of nitrofurantoin-induced anaphylactic reaction. The clinical features include fever, dyspnoea and tachypnoea, cough, which is often non-productive, basal crepitations, and occasional chest pain. There may be wheezing. The chest radiograph may be normal or show basal pulmonary alveolar infiltrates with or without pleural effusion and septal lines (Israel and Diamond, 1962; Satter, 1966; Strauss and Griffin, 1967; Nicklaus and Snyder, 1968; Ngan, Millard, Lant, and Trapnell, 1971).

The clinical and radiological signs clear after drug withdrawal. Long-term nitrofurantoin has been implicated as a cause of chronic interstitial lung disease (Murray and Kronenberg, 1965; David, Andersen, and Stickler, 1968) and may produce subacute pulmonary involvement (Sollaccio, Ribaud, and Grace, 1966). This paper reports the acute changes in lung function produced in a patient with hypersensitivity to nitrofurantoin, and the results give some indication of the type of reaction in the lungs.

CASE REPORT

A retired panel beater, aged 71, was given nitro-

furantoin, 300 mg daily, for dysuria and urinary frequency. After taking 900 mg he noticed dyspnoea, headache, nausea, and palpitations which subsided within 48 hours after he stopped taking the drug. There was no chest pain or wheezing. He was taking no other drugs. Two days later he took another 300 mg and developed moderate dyspnoea, malaise, shivering, and vomiting. He stopped the drug and was referred to hospital on 8 February 1969 with a provisional diagnosis of pneumonia. He had smoked 10 cigarettes daily for many years. Exercise tolerance had been very good.

On examination he was mildly distressed with tachypnoea of 30 breaths per minute. Temperature was 38.3°C which settled after 14 hours, and crepitations were heard at both lung bases; wheezes were absent. He coughed mucoid sputum occasionally. Blood pressure was 140/65 mmHg and the pulse rate 120 per minute. There was no rash nor pruritus. There was second-degree prostatic enlargement.

A mobile chest radiograph on admission was normal, as were subsequent standard radiographs. Haemoglobin was 14.7 g/100 ml; white cell count 10,000/mm³; neutrophils 54%; lymphocytes 28%; eosinophils 15%; monocytes 2%; basophils 1%. White cell count 48 hours later was 10,500/mm³; neutrophils 72%; lymphocytes 22%; eosinophils 2%; monocytes 3%; basophils 1%. Serum creatinine was 1.5 mg/100 ml. Serum electrolytes, bilirubin, glutamic oxaloacetic transaminase, alkaline phosphatase, protein electrophoresis, and urine microscopy were normal. Schumm's test was negative. The electrocardiogram was normal. Prostatic needle biopsy showed glandular hyperplasia.

Acute nitrofurantoin lung reaction was suggested by rapid resolution of the clinical picture and blood eosinophilia. Nine days later the patient was quite well and the lungs were normal to examination. A challenge of 200 mg of nitrofurantoin was given and 8 hours later mild dyspnoea with severe nausea and vomiting occurred. These symptoms resolved in 12 hours. Crepitations were again audible at the lung bases and persisted for three days. Less than 24 hours after challenge the white cell count was 16,000/mm³; neutrophils 79%; lymphocytes 15%; eosinophils 2%; monocytes 4%. There was a moderate number of sputum eosinophils (May Grünwald strain). The chest radiograph was normal. The white cell count 48 hours after challenge was 10,000/mm³; neutrophils 56%; lymphocytes 17%; eosinophils 24%; monocytes 2%. Two days later the blood picture was normal. Over the ensuing three years he remained well with normal clinical and radiological pulmonary findings.

PHYSIOLOGICAL FINDINGS

Baseline lung function studies (study A) were made nine days after admission. The challenge was given after this procedure and the studies were repeated 22 hours later (study B). Spirometry and lung volumes were measured nine weeks later (study C). More detailed studies were made three years later (study D).

Standard spirometric measurements of one

second forced expiratory volume (FEV_{1.0}) and vital capacity (VC) were made with a Godart spirometer and repeated 10 minutes after orciprenaline inhalation. Lung volumes were measured by closed-circuit helium dilution (Meneely and Kaltreider, 1949). Physiological dead space to tidal volume ratio (V_D/V_T), carbon monoxide transfer factor (TF) and alveolar arterial (A-a) oxygen gradient were made under steady state conditions (Holland and Blacket, 1958) and repeated after 10 minutes breathing 100% oxygen. Blood gas tensions were measured with a Radiometer triple electrode system and estimation of fractional carbon monoxide uptake (Fco) was by the method of Filley, MacIntosh, and Wright (1954). Static lung elastic recoil was measured with an oesophageal balloon and lung resistance (RL) was determined by the subtraction method (Mead and Whittenberger, 1953). Dynamic compliance (C_{dyn}) was measured by the method of Woolcock, Vincent, and Macklem (1969).

Lung function data are shown in Tables I, II, and III. Spirometry shows airways obstruction presumably related to pre-existing lung disease reflecting his smoking habits. The drug reaction produced no change in large airways calibre.

TABLE I
MEASUREMENT OF SPIROMETRY AND LUNG VOLUMES

	Study A	Study B	Study C	Study D
FEV ₁	2.30	1.55	2.45	2.55
VC	3.35 (88.3)	2.35 (62)	3.33 (87.8)	4.02 (107.8)
FEV ₁ /VC	68.7%	65.9%	73.6%	63.4%
FRC	3.393 (86.4)	3.168 (80.6)	2.972 (75.6)	4.179 (104.9)
RV	2.217 (87.3)	2.331 (91.8)	1.915 (75.4)	2.507 (97.4)
TLC	6.113 (95.4)	5.045 (78.7)	5.626 (87.8)	6.533 (102.5)

FEV₁=one second forced expiratory volume; VC=vital capacity; FRC=functional residual capacity; RV=residual volume; TLC=total lung capacity. Volumes are in litres ATPS. The values in brackets are percentages of the predicted normal values of Goldman and Becklake (1959).

TABLE II
MEASUREMENT OF GAS EXCHANGE

	Study A		Study B		Study D		Predicted Normal
	Air	100% O ₂	Air	100% O ₂	Air	100% O ₂	
Pao ₂	66.0	489.0	50.0	270.0	74.0	550.0	85
Paco ₂	40.0	45.5	32.0	39.0	39.0		35-45
pH	7.394	7.382	7.42	7.387	7.370	7.390	7.36-7.42
RQ	0.89		0.81		0.71		0.70-0.90
TF	18.0		10.9		10.1		17-35
A-a gradient	41.0		63.0		25.0		< 15
Fco	33%		22%		31%		35%
V _D /V _T	0.517	0.584	0.562		0.462		0.3 ± 0.03
Respiratory rate	24.0	25.0	35.0		25.0	23.0	
VE	10.3	9.5	15.6	15.5	9.5	7.67	

Pao₂=arterial oxygen tension (mmHg); Paco₂=arterial carbon dioxide tension (mmHg); RQ=respiratory quotient; TF=steady state transfer factor for carbon monoxide (ml of carbon monoxide per minute per mmHg); Fco=fractional carbon monoxide uptake; A-a gradient=alveolar-arterial oxygen difference (mmHg); V_D/V_T=physiological dead space to tidal volume ratio; VE=minute ventilation (litres BTPS)

TABLE III
LUNG MECHANICS (STUDY D)

Static compliance	0.167 litres/cmH ₂ O
Dynamic compliance	0.169 litres/cmH ₂ O
Total lung resistance	2.75 cmH ₂ O/litre/second
Recoil pressure at TLC	28 cmH ₂ O
C _{dyn} (60 breaths/minute)	78.4%

There was no significant response to orciprenaline at any time. Lung volumes demonstrated lung restriction 22 hours and nine days after challenge (studies B and C) with recovery at three years (study D). Challenge was also followed by a fall in TF and arterial oxygen tension and an increase in respiratory rate, dead space ventilation, and A-a oxygen gradient. The patient was smoking immediately before study D but not before A and B; hence TF and Fco (study D) may have been affected by back pressure carbon monoxide effect. Reduction in TF was the only abnormality that persisted till three years after exposure to the drug.

DISCUSSION

This study shows that acute nitrofurantoin pulmonary reaction produces completely reversible changes in lung function, unless the persistently low steady state TF is regarded as significant. The process has been described as a form of pulmonary oedema, and crepitations were heard although there were no radiological changes. Our studies point to the site of the lesion at the alveolar level although small airways involvement cannot be excluded. The marked fall in TF and Fco (study B) may be due to predominant deterioration in the membrane component of diffusion as the change in V/Q relationships is probably not large enough to explain the magnitude of the change. There are some similarities to an Arthus reaction (Brander and Selroos, 1969). Descriptions are lacking of the pathology of acute nitrofurantoin reaction although in the chronic form with fibrosis there is lymphocytic and plasma cell alveolar wall infiltrate (Israel *et al.*, 1973). Liebow and Carrington (1966) showed alveolar damage with mononuclear cell infiltrate in penicillin hypersensitivity. Acute hypersensitivity to sulphadimethoxine (Fiegenberg, Weiss, and Kirshman, 1967) showed alveolar lumina filled with eosinophils and histiocytes without alveolar wall infiltrate.

This patient's clinical features are similar to those described earlier with symptoms developing after a latent interval which decreases with subse-

quent exposures (Khorsandian, Bremer, and Nodine, 1963; Muir and Stanton, 1963; Robinson, 1964). Rapid resolution of physical findings and blood eosinophilia is characteristic (Hailey, Glascock, and Hewit, 1969) but not invariable (Vaughan Jones and Goldman, 1968).

This reaction has many features common to those produced by para-aminosalicylic acid (Kalinowski, Lloyd, and Moyes, 1961; Smith and Zirk, 1961), penicillin (Reichlin, Loveless, and Kane, 1953), imipramine (Wilson, Gambill, and Sandifer, 1963), chlorpropamide (Bell, 1964), mephenesin (Rodman, Fraimow, and Myerson, 1958), azothioprine (Rubin, Baume, and Vandenberg, 1972), sulphasalazine (Jones and Malone, 1972), furazolidine (Cortez and Pankey, 1972), and sulphonamides (Fiegenberg *et al.*, 1967).

In this case a total dose of 1.4 g of nitrofurantoin caused no permanent damage. Arterial hypoxaemia was the most serious consequence of the severe physiological abnormalities which persisted for at least nine weeks.

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