Bronchiolitis obliterans organising pneumonia associated with the use of nitrofurantoin

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Abstract

The spectrum of nitrofurantoin lung injury continues to widen. The case histories presented of two patients who developed lung disease associated with the use of nitrofurantoin with histological features of bronchiolitis obliterans organising pneumonia (BOOP), a rare but recognised form of drug induced injury. The two middle aged women presented with respiratory symptoms after prolonged treatment with nitrofurantoin. Both had impaired lung function and abnormal computed tomographic scans, and their condition improved when nitrofurantoin was withdrawn and corticosteroid treatment commenced. The favourable outcome in these two patients contrasts with the fatal outcome of the two other reported cases of nitrofurantoin induced BOOP. We suggest that the previous classification of nitrofurantoin induced lung injury into “acute” and “chronic” injury is an oversimplification in view of the wide variety of pathological entities that have subsequently emerged.

(Thorax 2000;55:249–251)

Keywords: bronchiolitis obliterans organising pneumonia; drug induced pulmonary disease; nitrofurantoin

An increasing number of drugs are recognised as causing lung injury and the spectrum of their adverse effects is widening. A recognised but uncommon form of drug induced lung disease is bronchiolitis obliterans organising pneumonia (BOOP). We report two cases of nitrofurantoin induced pulmonary disease with histological features of BOOP.

Case 1

A 34 year old female non-smoker with recurrent urinary tract infections presented with increasing dyspnoea and cough over several months. She had been taking nitrofurantoin 50 mg at night for more than two years. She had no other significant exposures and was on no other medications. Examination was normal. The chest radiograph showed diffuse bi-basal reticulonodular shadowing. Baseline blood tests were normal, except for ANA 1:1280, with a diffuse staining pattern. Lung function tests showed forced expiratory volume in one second (FEV1) of 2.09 l with forced vital capacity (FVC) of 3.56 l (predicted 3.84 l, respectively). Carbon monoxide transfer factor (TLCO) was reduced to 67% predicted. High resolution computed tomographic (HRCT) scans of the thorax showed patchy peribronchial interstitial thickening, especially of the medium and small sized bronchi, with very little fibrosis. Open lung biopsy specimens showed that many respiratory bronchioles were distorted and largely occluded by fibroblastic tissue with associated mucus plugging and outgrowth of respiratory epithelium into surrounding alveolar tissue, consistent with BOOP. In the absence of other factors a diagnosis of nitrofurantoin induced pulmonary disease was made and the drug was discontinued. Prednisone 30 mg per day, gradually reducing over nine months, resulted in significant symptomatic improvement, significant improvement in lung function (FEV1 3.56 l, FVC 4.20 l, TLCO 82% predicted), and considerable but incomplete clearance of interstitial changes on the HRCT scan.

Case 2

A 50 year old female non-smoker with recurrent urinary tract infections gave a two month history of worsening dyspnoea, fatigue, anorexia, and cough with fevers and night sweats for three weeks. There was no history to suggest an underlying connective tissue disorder. She had been taking nitrofurantoin 50 mg at night regularly for one year. On examination she was tachypnoeic and tachycardic with a wide alveolar-arterial gradient (9.1 kPa). Blood count and renal and liver function were normal, erythrocyte sedimentation rate (ESR) was 81 mm/h, and the ANA was 1:1640 with anti dsDNA negative. Lung function tests showed FEV1 of 0.82 l and FVC of 0.84 l (predicted 2.87 and 3.77 l, respectively). TLCO could not be measured because of breathlessness. An HRCT scan of the thorax showed patches of “ground glass” opacity, interstitial fibrosis with traction bronchiectasis, and scattered areas of dense consolidation (fig 1). Transbronchial biopsy specimens showed loose immature fibrous tissue within air spaces and incorporated into the interstitium, a patchy interstitial infiltrate of mixed inflammatory cells including lymphocytes, plasma cells, and a few eosinophils, and prominent hyperplasia of type II pneumocytes. Pieces of airway wall showed inflammation with peri-airway fibrous and outgrowth of respiratory epithelium into fibrotic lung tissue. The appearance was consistent with BOOP/diffuse alveolar damage. The diagnosis of nitrofurantoin induced pulmonary disease was made; the drug was withdrawn and prednisone 40 mg daily reducing slowly to baseline 10 mg daily was given over three months. At three months a repeat
HRCT scan showed marked reduction of the ground glass opacities and areas of consolidation, but with persistent interstitial fibrosis. Repeat lung function tests showed FEV₁ had improved to 2.88 l (100% predicted) with FVC 2.89 l (77% predicted) and TLCO 66% predicted. The patient was subsequently weaned off oral steroids with no clinical, radiological, or physiological evidence of relapse.

Discussion
We conclude that both patients had nitrofurantoin induced pulmonary disease on the grounds that there was a lack of an alternative explanation for their lung disease and a good response to drug withdrawal and treatment with an oral corticosteroid. We acknowledge that BOOP of other causes may respond well to corticosteroid treatment, but there was no disease recrudescence on steroid reduction and withdrawal. The establishment of a firm aetiological relationship would require re-challenge with nitrofurantoin. This was considered inappropriate in view of the severity of pulmonary impairment on presentation and the residual and irreversible changes on the HRCT scan.

Relatively few pharmaceutical agents have been associated with BOOP. These include amiodarone, acebutalol, nilutamide, cephalosporins, barbiturates, and cocaine. There are only two previously reported cases of BOOP attributable to nitrofurantoin use. Both patients were elderly ex-smokers with symptoms of 3–4 weeks duration and both responded well to initial corticosteroid treatment, but rapid tapering led to an irreversible decline and death after failure to respond to increased steroid dosage. Details of drug treatment were not included in the report.

The course of the disease in our patients was rather different. Both were maintained on medium to high dose prednisone initially, gradually reducing over months, and the duration of treatment may have been important in terms of the improved outcome. They were weaned off oral steroids without clinical, radiological, or physiological evidence of relapse.

Nitrofurantoin induced pulmonary disease may present in many forms including BOOP, diffuse alveolar damage, vasculitis, interstitial fibrosis, pleural and airways disease, and pulmonary haemorrhage. A final common toxic pathway has not been postulated. Nitrofurantoin induced pulmonary disease may result from immune mediated injury or via hydroxyl radical generation with subsequent free oxidant damage. The reduced incidence with the addition of the antioxidant ascorbic acid to nitrofurantoin preparations and results of in vitro studies suggest that this and other antioxidants may significantly reduce toxicity.

Initial reports suggested that the duration of nitrofurantoin treatment dictated the disease pattern. The “acute” reaction was characterised by marked constitutional symptoms including rash, fever, arthralgia, fatigue, together with pulmonary symptoms of dry cough and dyspnoea. The “subacute” and “chronic” forms were more insidious, with increased eosinophil count, raised ESR, and vasculitis and interstitial inflammation on histological examination, consistent with a type III immune response. Increased immunoglobulin levels, hepatic transaminases and ANA titres (the so called “drug induced lupus syndrome”) was associated with a degree of irreversible fibrosis. Some early reports of biopsy specimens from a patient with nitrofurantoin induced lung disease which predate the recognition of idiopathic BOOP as an independent entity are suggestive of a BOOP-like pattern. Cohen suggested that BOOP may be a precursor to chronic lung fibrosis, an early and potentially reversible phase in the spectrum of fibrosing lung disease. However, both patients in this report had residual radiological abnormalities although the remaining functional abnormalities were minor. The subsequent variety of

Figure 1  (A) Mid thoracic HRCT scan in case 2 showing small residual areas of normal lung, extensive interstitial fibrosis with traction bronchiectasis most marked in the right middle lobe, patchy ground glass opacity, and areas of dense consolidation. (B) Equivalent HRCT scan three months after withdrawal of nitrofurantoin and commencement of treatment with prednisone showing extensive but incomplete clearance of abnormalities.
LETTERS TO THE EDITOR

Systematic review of antistaphylococcal antibiotic therapy in cystic fibrosis

McCa\textsuperscript{1}ffery et al\textsuperscript{1} conclude that “antistaphylo-
coccal treatment achieves sputum clearance of \textit{Staphylococcus aureus} in patients with
cystic fibrosis . . . ” and that prophylactic
treatment in young children is “ . . . likely to
be of clinical benefit”.\textsuperscript{2} These positive conclu-
sions are based on the results of a study
which has important methodological
problems. Neither the introduction nor the
methods section of this review state what hypo-
theses the review set out to test, the criteria
used to decide whether a study was suitable
for inclusion, outcomes to be studied in the
review, or methods used to assess the
methodological quality of included studies.
Systematic reviews differ from narrative
reviews in that they test hypotheses using a
methodology which is well described.\textsuperscript{3} The
authors have described their search strategy,
which is based on that developed by the
Cochrane Collaboration, to identify ran-
donised controlled trials. The authors have,
however, included a number of studies in
their review which are not randomised
controlled trials. It is not clear from the
information provided whether their search
strategy is sensitive enough to identify all
possible relevant studies.

The authors base their conclusions on the
results of just two randomised controlled trials,
involving only 66 children, with a maximum
follow up of two years.\textsuperscript{4} All of these children
were under seven years of age (most under
two years) and had upper respiratory samples
taken, not sputum. Of the other studies
included in one of the randomised controlled
trials, only two randomised controlled trials
actually reported the prevalence of \textit{S aureus}
in respiratory secretions. The larger study by
Weaver et al\textsuperscript{4} reported that the prevalence of \textit{S
aureus} was reduced with prophylaxis but
“clearance” was not achieved from nose and
throat swabs.

The important issues for cystic fibrosis
patients and their families are not eradication
of an organism but fewer symptoms, im-
proved lung function, and prolonged survival.
None of the studies described in the review
addressed these. “This objective is consistent
with the view of the authors of the Cochrane Col-
laboration Handbook who recognise that sys-
tematic reviews can have different motiva-
tions, one of which is the resolution of conflict
evidence.” Indeed, it is probably difficult to
define systematic reviews as formally as Smyth
\textit{et al} (and others) have proposed as the science of systematic
reviewing is undergoing continuous development.
More systematic reviews are being performed
now than ever before (a Medline search look-
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\footnotesize{\textsuperscript{1} McCaffery K, Olver RE, Franklin M, \textit{et al.} \textit{Systematic review of antistaphylococcal antibiotic therapy in cystic fibrosis. Thorax 1999; 54:380–8.}


\textsuperscript{3} Weaver LT, Green MR, Nicholson K, \textit{et al.} Prognosis in cystic fibrosis treated with con-

\textsuperscript{4} Schlesinger E, Muller W, von der Hardt H, \textit{et al.} Continuous antistaphylococcal antibiotic treat-
ment in young children with cystic fibrosis. 9th International Cystic Fibrosis Congress 1984;
4.14(abstrat).

\textsuperscript{5} Harrison CJ, Marks MI, Welch DF. A multicen-
tric comparison of related pharmacologic features of cephalaxin and dicloxacillin given for


AUTHORS’ REPLY Smyth \textit{et al} have listed a number of features that they regard as being essential
to systematic reviews. In particular, they suggest that systematic reviews should always test hypotheses.
However, a clear understanding of the existing evidence is necessary for the generation of valid hypo-
theses and, in our view, this is best achieved by systematic reviewing. Indeed, many im-
portant systematic reviews published in major clinical journals do not specifically test
hypotheses, but study the current evidence in order to identify the state of existing knowl-
edge and to define areas for further research.4 This objective is consistent with
the view of the authors of the Cochrane Col-
laboration Handbook who recognise that sys-
tematic reviews can have different motiva-
tions, one of which is the resolution of conflict
evidence. Indeed, it is probably difficult to define systematic reviews as
formally as Smyth \textit{et al} (and others) have proposed as the science of systematic
reviewing is undergoing continuous development.
More systematic reviews are being performed
now than ever before (a Medline search look-

\footnotesize{\textsuperscript{1}4 Holmberg L, Boman G, Bottinger LE, \textit{et al.} Adverse reactions to antistaphylococcal antibiotics: analysis of 921 reports. Am J


symptoms, improved lung function, and prolonged survival. However, this should not inhibit the use of laboratory based outcomes which could influence clinical decision making until appropriate clinical data are available. Indeed, given the high predictive value of outcomes in children in identifying pathogen in bronchoalveolar lavage fluid (sensitivity and specificity of 90%), we feel the evidence we have defined in support of Staphylococcus aureus from the upper or lower respiratory tract with anti-staphylococcal antibiotics does suggest that this therapeutic intervention is likely to be of clinical benefit, although we strongly support their argument that properly designed studies are needed to confirm this hypothesis.

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Therapeutic ratio of inhaled fluticasone

I read with interest the recent article by Meijer et al and colleagues on the effects of inhaled fluticasone and prednisolone on clinical and inflammatory parameters in patients with asthma.2 Rather than focusing on the differences between oral and inhaled corticosteroid, I believe that a more important finding is the effect of a fourfold increase in the dose of fluticasone on the therapeutic ratio. For airway parameters there were no significant differences in the effects on bronchial hyperresponsiveness to methacholine and adenosine monophosphate or on sputum eosinophils between the two doses of inhaled fluticasone in doses of 500 µg and 2000 µg per day. However, for systemic bioactivity markers there were significant differences between the two doses of fluticasone on serum cortisol levels and blood eosinophils. Taken together these findings suggest that, at least for effects on airway hyperresponsiveness and inflammation, the therapeutic ratio for fluticasone declines sharply above a watershed dose of 500 µg per day. This result is perhaps not surprising, given the high glucocorticoid topical potency for in vitro anti-inflammatory activity with fluticasone.

It is also important to point out that the study by Meijer et al was performed using fluticasone delivered via a Diskhaler dry powder inhaler device, which delivers a twofold lower respirable fine particle dose than a fluticasone propionate powder inhaler. This is due to the larger particle size from the fluticasone dry powder inhaler. Hence, increasing the nominal dose of fluticasone dry powder may result in a proportionately greater delivery of larger particles to the central airways and consequently to a less than expected impact on small airway inflammation. The lower fine particle dose of fluticasone dry powder will also result in reduced lung bioavailability, as shown by a fivefold greater degree of adrenal suppression compared with the same nominal dose of fluticasone delivered via a pressurised metered dose inhaler with spacer device.2 The use of fluticasone in a dose of 500 µg/day via a dry powder inhaler would therefore explain the absence of any significant suppression of blood eosinophils or serum cortisol in their study. This does not mean that fluticasone propionate dry powder in a dose of 5000 µg/day is not systemic but rather this is recently published data with this dose of fluticasone given via a Diskhaler reported significant suppression of 24 hour urinary cortisol excretion (33% reduction) and peripheral blood lymphocyte glucocorticoid receptor mRNA expression (71% reduction) during steady state dosing in asthmatic subjects.

Another finding in the study by Meijer et al was the relatively greater effect on bronchial hyperresponsiveness to adenosine monophosphate than to methacholine challenge with both oral and inhaled corticosteroid after two weeks. Similar findings have been reported after two weeks of treatment with inhaled budesonide powder in a dose of 1600 µg/day.3 In vivo modulation of glucocorticoid receptor mRNA by inhaled fluticasone propionate (S13–9). The concept that the improvement continues for a longer period than that of prednisolone on clinical and inflammatory parameters in patients with asthma. Thorax 1999;54:894–9.

adrenosine is interesting, but we are unaware of any data to substantiate this. In fact, in a study by Weersink and colleagues, the same difference between the two bronchoconstrictor agents held true for six weeks instead of the two weeks of fluticasone treatment in the current study.

It is interesting to debate whether the insufficient effect of inhaled steroids in patients with severe asthma is due to lower availability in the peripheral airways, as Dr. Lipworth suggests, or, for instance, to a decreased sensitivity to steroids—either per se or as a result of increased inflammation and associated cytokine load. The suggestion by Dr. Lipworth that one would result in a relatively smaller net effect of systemic steroids compared with inhaled steroids, especially in the more obstructed patients, but this does not agree with our clinical impression. In fact, the finding of a superior effect of the inhaled cortico-steroid over oral prednisolone (30 mg for two weeks) in our study rather suggests a contrary mechanism, perhaps compatible with a higher effectiveness of the lipophilic compound fluticasone at the level of the epithelium and (sub)mucosa than of systemic prednisolone, even if only in the larger airways. Nevertheless, we are careful not to extrapolate our findings beyond the devices and populations studied. There are, however, in addition to ours, a few other studies which suggest that inhaled corticosteroids may have an effect at least as great as prednisolone in asthma exacerbations. 4

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1 Meijer RJ, Kerstjens HA, Arends LR, et al. Effects of inhaled fluticasone and oral pred-

nisolone on clinical and inflammatory para-


2 Wilson AM, Sims EJ, Orr LC, et al. Differences in lung bioavailability between different prop-


5 Ghaffar O, Hamid Q, Renzi PM, et al. Constitut-


7 DiFranco A, Giannini D, Bartoli ML, et al. Anti-inflammatory effect of prednisone vs. fluta-

casone propionate in the treatment of moderate

exacerbations of asthma as assessed by spe-


“Systematic review” of asthma education studies

We were disappointed that Sudre et al felt there was insufficient documentation and excessive variability in studies of education programmes for adults with asthma published between 1979 and 1998. We feel that their conclusion is largely because they did not perform a rigorous systematic review of papers in this area. Systematic reviews of research evidence are undoubtedly invaluable scientific activities. They establish whether scientific findings are consistent and can be generalised across populations, settings, and other variations. Systematic reviews should be based on the “gold standard” of published randomised clinical trials. However, in the 77 trials reported Sudre et al included 35 studies which were not randomised controlled trials. They also give no information about which interven-

tions were found to have statistically significant effects. They include a study which simply asked patients who had received audio-

visual information or written information and did not have any intervention, a study which has not been published, 3 and interventions assessing the use of psychotherapy and yoga for asthma patients, which seem outside the criteria for inclusion in the review. Another four studies they include are excluded from the Cochrane reviews of patient education on the grounds that they are not educational interventions. As mentioned above, our own randomised controlled trial on personalised patient education for asthma delivery in fourbooklets over three months (reference 65) is correctly quoted as consisting of “a 10 minute encounter with a physician”. We are concerned that other studies referenced may also have been incorrectly classified.

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1 Sudre P, Jacquettem S, Uldry C, et al. Objectives, methods and content of patient education pro-


3 Simonian YH. The efficacy of education and resilience training on asthma patients’ self-


4 Deter HC. Cost-benefit analysis of psychoso-


6 Gibson PG, Coughlan J, Wilson AJ, et al. The effects of limited (information only) patient educa-


8 Osman LM, Abdalla MI, Beattie JAG, et al. Reducing hospital admission through compu-

BOOK REVIEWS


This text is a thorough but concise overview of clinical tuberculosis presented as a well structured series of cases with clearly reproduced radiographs, computed tomographic scans, and slides. Each case is complemented by a short pertinent discussion clarifying any points of interest or debate. A carefully chosen chapter layout sequentially introduces the reader to the most challenging and interesting aspects of the disease and also provides an easy reference framework.

The authors’ obvious wealth of experience allows readers with a more limited exposure to learn something of the more unusual manifestations of infection, including an extensive range of extrapulmonary and multisystem disease. The complex matter of antituberculous treatment in the emergent group with drug resistant mycobacterial infection, comorbidity, or compliance problems is tackled in some depth, highlighting potential pitfalls and explaining, in a real clinical context, the reasons behind the decisions made.

The difficulties associated with the diagnosis and management of tuberculosis in patients with human immunodeficiency virus are well illustrated, but not exhaustively covered, in a chapter whose commentary sections are particularly full and instructive.

Most of the 120 featured case presentations have a short list of affiliated references aimed to guide, rather than delineate in detail, further research of the points of interest raised.

The format of the book ensures an enjoyable and pragmatic approach to learning about tuberculosis, thus making it distinctly relevant to all those involved in the medical care of patients with the condition, especially at a training level. It would be an ideal accompaniment to existing formal textbooks.—ILJ


This is one of a series of publications under the collective heading “Progress in Inflammation Research” to which some of the European heavyweights in asthma research have contributed chapters. All the asthma drugs are included with the notable exception of the anticholinergic agents, although I found the title a little misleading as the in vivo anti-inflammatory effects of some of the drugs discussed remains contentious. However, from the opening chapter it becomes apparent that investigations into the pathophysiology of, and the effects of treatment on, asthma have played an important part in defining the inflammatory mechanisms. The “commonly” used asthma medications are discussed initially with Peter Barnes giving an erudite synopsis of the anti-inflammatory effects of corticosteroids. The next two chapters deal with the putative anti-inflammatory effects of phosphodiesterase inhibitors and β1 adrenoceptor agonists, although the chapter on phosphodiesterase inhibitors concentrated on the different isoenzymes and thus was heavy going with little discussion of their anti-inflammatory effects and no concluding summary. Despite theophylline being available for at least 40 years, I was struck by the paucity of clinical data available regarding its efficacy and in vivo anti-inflammatory effect (if at all). This is presumably because it is not profitable for pharmaceutical companies to investigate the drug further. The mast cell stabilisers are considered next, and the last third of the book deals with leukotriene antagonists and discusses other novel potential anti-inflammatory agents including anti-IgE agents, cytokines and adhesion molecule antagonists.

Several of the chapters are interesting and well written with well laid out tables and graphs, although some have several annoying typographical errors. The book does provide a good summary of the anti-inflammatory effects of present and potential future asthma medications and would act as a good reference source for departments or individuals with an interest in this field.—JB

CORRECTIONS

UK Pulmonary Vascular Units

In the list of UK Pulmonary Vascular Units given at the end of the review article on “Primary pulmonary hypertension” by A J Peacock which appeared in the December issue of Thorax (1999;54:1107–18), the address for Dr Simon Gibbs should have included the Imperial College School of Medicine which includes Hammersmith, Brompton and Harefield hospitals.

Atrial septostomy in pulmonary vascular disease

In the editorial entitled “Role of atrial septostomy in the treatment of pulmonary vascular disease” by R J Barst which appeared on pp 95–6 of the February issue of Thorax, there was an error in figure 1. The correct version is reproduced below, showing that in “non-responders” the PAP is increased or unchanged. The publishers apologise for this error.

NOTICES

Cardiovascular Disease Prevention V

A conference entitled “Cardiovascular Disease Prevention V” will be held on 4–7 April 2000 at the Conference Centre, Kensington Town Hall, London. For further information contact The Secretariat, Hampton Medical Conferences Ltd, 127 High Street, Teddington, Middlesex TW11 8HH, UK. Telephone +44 (0)181 977 0011. Fax +44 (0)181 977 0055. email hmc@hamptonmedical.com

British Association for Lung Research

The British Association for Lung Research (BALR) Spring Meeting entitled “Inflammation Control: A Goal for the Millenium” will be held on 18 April 2000 at the Wills Hall, University of Bristol. For further information contact Dr Lynne Armstrong, The Lung Research Group, University of Bristol Medical School Unit, Southmead Hospital, Westbury on Trym, Bristol BS10 5NB, UK. Telephone +44 (0)117 950 5348. Fax +44 (0)117 950 5018. email Lynne.Armstrong@bristol.ac.uk

Letters to the editor, Book reviews, Notices, Corrections

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