Bronchiolitis obliterans organising pneumonia associated with the use of nitrofurantoin

R J Cameron, J Kolbe, M L Wilsher, N Lambie

Abstract

The spectrum of nitrofurantoin lung injury continues to widen. The case histories are 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impaired lung function and abnormal computed tomographic scans, and their condition improved when nitrofurantoin was withdrawn and corticosteroid treatment commenced.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.

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 “velcro” crackles. Arterial blood gas measurements showed hypoxia (Pao₂, 6.5 kPa) 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 2.33 l, 2.87 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 recurrence 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 titre (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.
pathological entities now shown to be caused by nitrofurantoin suggests that these early categorisations are an oversimplification.

The initial interest in nitrofurantoin induced lung disease has waned as more suitable less toxic agents have been found for chronic urinary infection. However, the drug remains generally available in spite of its high toxic profile and clinicians need to be aware of the spectrum of associated lung disease.


LETTERS TO THE EDITOR

Systematic review of antistaphylococcal antibiotic therapy in cystic fibrosis

McCaffrey et al conclude that “antistaphylococcal treatment achieves spumt clearance of Staphylococcus aureus in patients with cystic fibrosis . . .” and that prophylactic treatment in young children is “ ... likely to be of clinical benefit”. These positive conclusions 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 hypotheses 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. The authors have described their search strategy, which is based on that developed by the Cochrane Collaboration, to identify randomised 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. All of these children were under seven years of age (most under two years) and had upper respiratory infection samples taken, not sputum. Of the other studies described as randomised, one used alternate allocation (and so was not randomised) and one reported further outcomes in patients included in one of the randomised controlled trials. Only two randomised controlled trials actually reported the prevalence of S aureus in respiratory secretions. The larger study by Weaver et al reported that the prevalence of 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, improved 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 Collaboration Handbook who recognise that systematic reviews can have different motivations, one of which is the resolution of conflicting evidence. Indeed, it is probably difficult to define systematic reviews as formally as Smyth et al (and others) have proposed as the science of systematic review is undergoing continuous development. More systematic reviews are now being performed than ever before (a Medline search looking for “systematic review” in titles and abstracts presents 4158 citations in the last 10 years, 1538 (37%) of which are in the last two), with reviewers defining their methods according to the problem in question.

Again, because of the nature of the field being studied, we had purposely not defined stricter criteria for study selection or drawn up a preselected list of outcomes of interest. As the area under investigation was largely unknown, we felt such criteria could limit our search. Also, in the absence of any significant background information, we were uncertain if such a choice of outcomes could be motivated objectively. Indeed, if we had arbitrarily drawn up a list of outcomes that were of interest to us, we would have missed a number of outcomes that others have used and which could be of potential interest to readers when designing clinical trials in the future. We did not use quality scores because there is little objective evidence to support the use of quality scoring in systematic reviews. Many of the scoring systems have not been developed with sufficient rigour and could add the analyst’s bias to the results. A recent review of a random sample of 240 meta-analyses showed that less than half assessed trial quality. However, we note that newer techniques such as meta-regression may provide better alternatives in the future.

As we were principally interested in randomised controlled trials (RCTs), we used a search strategy that has been well validated for the recall of such trials. However, as before, we wanted to present an analysis of outcomes of both RCTs and non-RCTs because we felt this would make our conclusions more objective. This was supported by the authors of the Cochrane Collaboration Handbook. Smyth et al state quite rightly that the important issues for cystic fibrosis patients and their families are not eradication of an organism but fewer


Authors’ Reply Smyth 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 hypotheses and, in our view, this is best achieved by systematic reviewing. Indeed, many important 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 knowledge and to define areas for further research. This objective is consistent with the view of the authors of the Cochrane Collaboration Handbook who recognise that systematic reviews can have different motivations, one of which is the resolution of conflicting evidence. Indeed, it is probably difficult to define systematic reviews as formally as Smyth et al (and others) have proposed as the science of systematic reviewing is undergoing continuous development. More systematic reviews are now being performed than ever before (a Medline search looking for “systematic review” in titles and abstracts presents 4158 citations in the last 10 years, 1538 (37%) of which are in the last two), with reviewers defining their methods according to the problem in question.

Again, because of the nature of the field being studied, we had purposely not defined stricter criteria for study selection or drawn up a preselected list of outcomes of interest. As the area under investigation was largely unknown, we felt such criteria could limit our search. Also, in the absence of any significant background information, we were uncertain if such a choice of outcomes could be motivated objectively. Indeed, if we had arbitrarily drawn up a list of outcomes that were of interest to us, we would have missed a number of outcomes that others have used and which could be of potential interest to readers when designing clinical trials in the future. We did not use quality scores because there is little objective evidence to support the use of quality scoring in systematic reviews. Many of the scoring systems have not been developed with sufficient rigour and could add the analyst’s bias to the results. A recent review of a random sample of 240 meta-analyses showed that less than half assessed trial quality. However, we note that newer techniques such as meta-regression may provide better alternatives in the future.

As we were principally interested in randomised controlled trials (RCTs), we used a search strategy that has been well validated for the recall of such trials. However, as before, we wanted to present an analysis of outcomes of both RCTs and non-RCTs because we felt this would make our conclusions more objective. This was supported by the authors of the Cochrane Collaboration Handbook. Smyth et al state quite rightly that the important issues for cystic fibrosis patients and their families are not eradication of an organism but fewer
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 oral steroids in children for identifying pathogen in bronchoalveolar lavage fluid (sensitivity and specificity of 90%), it is 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 respiratory fine particle dose than a fluticasone propionate powder dry 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 lower degree of adrenal suppression compared with the same nominal dose of fluticasone delivered via a pressurised metered dose inhaler with spacer device. 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 500/250 µg/day is not systemically active; indeed, the authors 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 patients. Another finding in the study by Meijer et al. was the relatively greater effect on bronchial hyperresponsiveness to adenosine monophosphate or on sputum eosinophils when fluticasone were used, we are careful not to overinterpret where the decline in the therapeutic ratio starts with this drug. Unfortunately, in the study by Meijer et al. on patients with relatively mild asthma to more severe asthmatic patients in whom altered airway geometry may cause a reduction in lung delivery and lung bioavailability from narrowed peripheral small airways. Also, their results may be specific to the unique drug/device interaction of fluticasone propionate given via the dry powder inhaler, and further studies are needed to look at the dose-response relationship of the therapeutic ratio using more efficient delivery systems such as a pressurised metered dose inhaler with spacer.

**Therapeutic ratio of inhaled fluticasone**

I read with interest the recent article by Meijer and colleagues on the effects of inhaled fluticasone and prednisolone on clinical and inflammatory parameters in patients with asthma.

Further, this study is also of clinical interest in our article. Although we found no significant dose difference in FENO, adenosine monophosphate and methacholine hyperresponsiveness with inhaled corticosteroids and beta-agonists on the bronchial hyperresponsiveness in children. We agree that the improvement in hyperresponsiveness with steroid treatment can continue for a longer period than that of methylxanthine bronchodilators. However, the treatment period was relatively short and one cannot exclude the possibility that, with more sensitive markers we clearly demonstrate this. We accept the notion that, with more sensitive markers of bioavailability, an effect might have been detectable. It is also conceivable that differences in bronchial hyperresponsiveness between the doses of inhaled fluticasone may have become apparent with a longer duration of treatment. Finally, it is important not to extrapolate the results of the study by Meijer et al. on patients with relatively mild asthma to more severe asthmatic patients in whom altered airway geometry may cause a reduction in lung delivery and lung bioavailability from narrowed peripheral small airways. Also, their results may be specific to the unique drug/device interaction of fluticasone propionate given via the dry powder inhaler, and further studies are needed to look at the dose-response relationship of the therapeutic ratio using more efficient delivery systems such as a pressurised metered dose inhaler with spacer.

**AUTHORS’ REPLY** We thank Dr Lipworth for his interest in our article. Although we found no significant dose difference in FENO, adenosine monophosphate and methacholine hyperresponsiveness with inhaled corticosteroids and beta-agonists on the bronchial hyperresponsiveness in children. We agree that the improvement in hyperresponsiveness with steroid treatment can continue for a longer period than that of methylxanthine bronchodilators. However, the treatment period was relatively short and one cannot exclude the possibility that, with more sensitive markers we clearly demonstrate this. We accept the notion that, with more sensitive markers of bioavailability, an effect might have been detectable. It is also conceivable that differences in bronchial hyperresponsiveness between the doses of inhaled fluticasone may have become apparent with a longer duration of treatment. Finally, it is important not to extrapolate the results of the study by Meijer et al. on patients with relatively mild asthma to more severe asthmatic patients in whom altered airway geometry may cause a reduction in lung delivery and lung bioavailability from narrowed peripheral small airways. Also, their results may be specific to the unique drug/device interaction of fluticasone propionate given via the dry powder inhaler, and further studies are needed to look at the dose-response relationship of the therapeutic ratio using more efficient delivery systems such as a pressurised metered dose inhaler with spacer.

**BRIAN J LIPWORTH**

**Asthma and Allergy Research Group,**

**Department of Clinical Pharmacology,**

**Ninewells Hospital and Medical School,**

**University of Dundee,**

**Dundee DD1 9SY, UK**
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 bronchonconstrictor 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 or greater efﬁcacy of the peripheral airways. 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 could result in a greater shorter 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 corticosteroid over oral prednisolone (30 mg for two weeks) in our study rather suggests a contrary mechanism, perhaps compatible with a higher effectiveness of the lipopholic 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 population 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.1


“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 interventions were found to have statistically signiﬁcant effects. They include a study which simply asked patients whether they preferred audiovisual information or written information and did not have any intervention,1 a study which has not been published, and interventions assessing the use of psychotherapy2 and yoga3 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 education4 on the grounds that they are not educational interventions. We are not surprised in noting that in 81% of projects assessed the background educational theory was not mentioned and few projects had a patient’s needs assessment performed.

While we accept that many of the studies reviewed had missing information on the form and duration of education, we are concerned that some of these studies may be being misquoted. As an example, our own randomised controlled trial on personalised patient education for asthma delivery in four booklets over three months (reference 65) is incorrectly quoted as consisting of “a 10 minute encounter with a physician”.5 We are concerned that other studies referenced may also have been incorrectly classiﬁed.


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 directly 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 β2 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

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 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)117 959 5348. Fax +44 (0)117 959 5018. email Lynne.Armstrong@bristol.ac.uk

UK Pulmonary Vascular Units

In the list of UK Pulmonary Vascular Units given at the end of the review article on “Pulmonary artery pressure” 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.

CORRECTIONS