

■ ASTHMA

## Are beta<sub>2</sub>-agonists the cause of airway hyper-responsiveness?

From Dr B. O. Hughes, MRPharmS

In Colin Deeney's stimulating review article about the possible negative effects of using of beta<sub>2</sub>-agonists in asthma (*PJ*, 12 August, p193–5), he refers to rebound airway hyper-responsiveness (AHR). AHR is a noted symptom following an acute asthma attack and clearly beta<sub>2</sub>-agonists are routine therapy in such situations. Is there any evidence that the AHR is due to the agonist rather than to the processes instigated by the acute exacerbation per se?

**Bryn Hughes**  
New Malden,  
Surrey

COLIN DEENEY, author of the article, responds: Airway hyper-responsiveness (AHR) is indeed a symptom of asthma and could confound any research. Studies have compared one group taking a beta<sub>2</sub>-agonist regularly with a control group. In these studies, the control group may have either been using a beta<sub>2</sub>-agonist on an "as needed" basis, not using a beta<sub>2</sub>-agonist at all, or using an inhaled corticosteroid.

After a given period, or over a series of periods, AHR was assessed in both groups using a provocative challenge (histamine, methacholine or allergen). The studies cited in the article I wrote found an increase in the response to these challenges in the active groups when compared with the control groups. Hence, the concern that beta<sub>2</sub>-agonists may increase AHR.

There have, however, been criticisms of the methodology, statistical analysis and interpretation with some of these papers. Furthermore, other studies have found no evidence of rebound AHR. In these studies the control also consisted of people with asthma and I am unaware of any study which has investigated whether a beta<sub>2</sub>-agonist may lead to AHR in people with no asthma. However, Girodet *et al*<sup>1</sup> studied human and guinea-pig isolated airways *in vitro*. They found that salbutamol inhibited contractions induced by low concentrations of acetylcholine but potentiated contractions induced by higher concentrations of acetylcholine. In addition, Loss *et al*<sup>2</sup> found rebound AHR in guinea pigs (with no

asthma) following a low dose of salbutamol, administered via subcutaneous osmotic minipumps. The rebound AHR followed challenge with the cholinergic agonists carbachol and methacholine (but not histamine). The hyper-responsiveness was more marked 24 hours after salbutamol cessation. The investigators suggest that the salbutamol may have therefore afforded some protection against the hyper-responsiveness. Now, if this is also the case in patients, when the beta<sub>2</sub>-agonist has waned, patients may perceive they need more due to rebound AHR.

While the debate continues as to the significance and relevance of these papers from a clinical perspective, the possibility that the S-enantiomer may be responsible for rebound AHR is of interest. The literature on beta<sub>2</sub>-agonist chirality and AHR suggests that some researchers, at least, have "moved on". Rightly or wrongly they have accepted the possibility that AHR increases with the S-enantiomer alone and are looking at using the S-enantiomer alone clinically. There may be commercial advantage for them in doing so, of course, even if the debate on rebound AHR remains inconclusive.

One reason that has been put forward as a mechanism for rebound AHR is a crossing of the bronchodilating and bronchoprotective pathways. Loss *et al* also suggest this or chirality as "attractive possibilities". Girodet *et al* propose that rebound hyper-responsiveness is mediated through a mechanism involving calcium channel activation. This was after pre-treatment of isolated airways with the calcium channel antagonist nifedipine suppressed the hyper-response. Furthermore, stimulation of cultured human airway smooth muscle cells with salbutamol amplified intracellular calcium concentration rise induced by acetylcholine.<sup>1</sup> Swystun *et al*<sup>3</sup> found indicators of an early asthmatic response as early as one hour after treatment with salbutamol. They therefore suggest that a combination of allergen exposure and beta<sub>2</sub>-agonist may induce both an early and late asthmatic response and this may lead to an increase in AHR. They also queried whether environmental allergen exposure is the reason why some studies have found rebound AHR while others have not. Proponents of Buteyko's hypothesis suggest that the use of a beta<sub>2</sub>-agonist leads to an increase in minute ventilation and that this in

turn leads to cooling and drying of the airways, increased allergen and irritant deposition, hypocapnia, and an increase in inflammatory factors, and thus, AHR.

### References

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■ HOMOEOPATHY

## Foundations still in good shape

From Mr L. N. Collin, MRPharmS

In responding to Richard Schmidt's letter (*PJ*, 19 August) I am reminded that the homoeopathy debate can be relied upon to recur with alarming regularity, somewhat like a bad case of malaria.

Dr Schmidt, having studied china officinalis in 'Kent's homoeopathic repertory', finds "3,800 conditions/ circumstances where it might be prescribed".

Most "provings" do yield myriads of symptoms and come from both observations of accidental poisonings and those experienced by actual provers. Thus, for example, 'Hahnemann's proving of arsenicum album',<sup>1</sup> on

eight healthy volunteers yielded 655 symptoms covering the mind, head, eyes, ears, nose, teeth, mouth and throat, stomach and abdomen, urinary and sexual organs — all meticulously recorded, and that was merely the first half of the proving. From this mass of symptoms, certain themes were evident which were strong in some individuals or present in many others, and these were assigned greater significance (shown in bold type or italics in 'Kent's repertory'). For example, "Mind, restlessness, night" and "Mouth, pain, burning" display striking keynotes of this remedy — strong characteristics of both the remedy provings and accidental ingestion of arsenic (possibly as a side effect of too much Fowler's solution — liquor arsenicalis, mentioned in the older pharmacopoeias). However, as Dr Schmidt mentions in his letter, this does not itself constitute evidence of the remedy's effectiveness in a clinical situation. To address this issue, the remedy is administered by reliable prescribers to sick people, according to the symptoms generated in the proving. As clinical experience grows, careful records are made of symptoms which are cured during the process of a real cure of the patient. Eventually a complete picture of the remedy emerges from all sources: toxicological literature, provings, and clinical observations.<sup>2</sup> It is this dynamic process which forms the basis of the information in the repertories and 'Materia medica'.

This does not, of course, cover the highly contentious issue of homoeopathic prophylaxis. Hahnemann, again, was the first person to test the maxim that an ounce of prevention is worth a pound of cure when he discovered

## Letters to the editor

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Letters that are critical of individuals, organisations or companies may be sent to the person or body concerned so that they are given a simultaneous right of reply. In these instances, the authors' identities will not be disclosed until publication, and publication will usually be delayed.

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that scarlet fever “found its preventative and curative means in belladonna”.<sup>3</sup> His skill was further tested successfully by the Asian cholera epidemic when three main remedies (camphor, veratrum album and cuprum)<sup>4</sup> were used to prevent cholera in the healthy, as well as treat the disease, depending on specificity of symptoms. Remedies chosen by such a group picture are called the genus epidemicus, and represent the essence of the disease. Interestingly, it was also found that people working in copper mines at the time seemed to have a natural immunity to cholera.

Finally, Dr Schmidt’s comment about the “implicit admission” by the Faculty of Homoeopathy, “that homoeopathy is not effective in either treating or preventing malaria” is incorrect. The statement put out by the Faculty refers to prevention only (because no published evidence can be cited) and not to treatment. The Faculty’s fact sheet, “Homeopathy and immunisation” (available at [www.truthhomeopathy.org](http://www.truthhomeopathy.org)), states that “well chosen homoeopathic remedies prescribed by trained practitioners, can successfully treat epidemics of infectious disease”.

#### Lawrence Collin

*Westcliff on Sea,  
Essex*

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3. Hahnemann, S. *Organon of the medical art*. Palo Alto, California: Birdcage Books, 1997, p119.
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#### ■ CONTROLLED DRUGS

### New CD regulations — advice please

From Mr F. Royle, MRPharmS and Miss J. Cram, MRPharmS

Recently, the regulations relating to prescriptions for Controlled Drugs were changed, permitting pharmacists to make alterations to otherwise legally valid prescriptions where technical information was missing.

We have some interesting points we would like to share with the wider membership after we both, separately, received incomplete prescriptions for schedule 2 CD medicines. Both the prescriptions

in question required the total quantity in words to be added, as permitted by the regulations.

The guidance provided by the Royal Pharmaceutical Society states that the amendment made by the pharmacist must be “attributable to them”. If a pharmacist alters a prescription and a balance is owed, or the stock has to be ordered, how does another pharmacist know who has amended that prescription, and is that pharmacist then obliged to make a supply?

If an alteration is made, and subsequently the patient chooses not to have his or her prescription dispensed at that pharmacy, is the next pharmacist who encounters the prescription obliged to dispense that prescription, given that he or she would not necessarily know who had made the alteration?

A clearly attributable amendment would presumably include a name, registration number and possibly even a contact telephone number and would take up a great deal of space on a prescription if completed properly. Is this practicable? What if the pharmacist who makes the amendment does not make it attributable to them in a clear enough manner?

We would be interested to hear the advice of the Society’s law and ethics department and of any other examples of a similar nature, as we are sure the points we have raised are not exhaustive.

#### Finlay Royle Julia Cram

*Cardiff*

PRIYA SEJPAL, professional ethics pharmacist, Royal Pharmaceutical Society, responds: Following the changes to the Misuse of Drugs Regulations 2001, as amended, pharmacists may make changes to CD prescriptions in certain defined circumstances, where the prescriber’s intentions are absolutely clear. (See *PJ*, 1 July, pp 25–9 or [www.rpsgb.org](http://www.rpsgb.org)). The pharmacist must ensure that the prescription is marked so that the amendment is attributable to them. The Regulations do not specify exactly how the prescription should be marked. A pharmacist may write their name, registration number or signature on the prescription, or could alternatively place an asterisk by the change and place a footnote on the script. The Society is currently awaiting further advice from the Home Office on issues surrounding

technical errors and a Law and Ethics Bulletin providing further guidance on this will be published in due course.

#### ■ COMPLIANCE AIDS

### Aids are not the solution to all problems

From Mrs E. Stanley, MRPharmS, and Dr C. G. Cable, MRPharmS

In his letter of 19 August (*PJ*, 19 August, p220), David Green highlighted some issues surrounding the use of compliance aids in patients who have not been properly assessed, to ascertain their individual needs and requirements. Described below is a case where an assessment showed a compliance aid was not necessary for a hospital patient on discharge.

A 70-year-old male was admitted to Western General Hospital with complex dermatological problems. On admission, the patient was taking three medicines but, seven months later at the discharge-planning stage, he was receiving 13 medicines. As the patient stayed alone in his own home, senior medical and nursing staff considered that a compliance aid was necessary to ensure medicines were taken correctly.

Discussions with the patient indicated that he was bright, intelligent and alert and viewed the introduction of a compliance aid as a further erosion of his independence — he was willing and felt competent to continue to administer his medicines without a compliance aid. The patient agreed that a medicine reminder chart would be helpful and that being able to arrange the medicines in an order that suited him would reduce confusion.

The patient’s views were discussed with medical staff, and it was agreed that an assessment of the patient’s ability to take his medicines independently should be carried out. The Western General Hospital operates a dispensing at bedside medicines lockers. A medicine reminder chart was produced for the patient and nurses were trained in the patient self-administration policy. One week before discharge, and under nursing supervision, the patient was responsible for administering his medicines and his ability to do this correctly was assessed daily. It became evident quickly that using the medicine reminder chart allowed the patient to administer

his own medicines and that a compliance aid was not necessary.

Before discharge, the patient’s community pharmacist was alerted to the current drug therapy and advised of the use of a medicine chart by the patient. The community pharmacist was willing to amend the reminder chart should further changes be made to the patients’ therapy.

This case demonstrates that there are alternatives to the use of compliance aids and that sharing pharmaceutical care between hospital and community pharmacy can result in tangible patient benefit. The capabilities of patients should be carefully assessed and the feasibility of incorporating the patient’s wishes explored.

#### Liz Stanley

*Dermatology Pharmacist*

#### Colin Cable

*Royal Pharmaceutical Society Fellow  
in Pharmaceutics  
Western General Hospital,  
Edinburgh*

#### ■ MURS

### MURs belong in pharmacists’ hands

From Mr J. Woodward, MRPharmS

Medicines use reviews justifiably belong in the hands of the community pharmacist. Pharmacists know their patients, are in constant contact with them. We are able to communicate in a way that puts the patient at ease. We are thorough, efficient and professional and, because we are used to working in a business environment, are naturally far better equipped to undertake such a task within a sensible time frame.

Can you imagine such a task being undertaken by a complete stranger? The first 15 minutes are going to be taken up by trying to gain the patient’s confidence. They are unfamiliar and inexperienced in dealing with the general public because of their office habitat.

#### John Woodward

*Acton Trussell,  
Stafford*

#### Broad spectrum

The Broad Spectrum feature is open to any reader. Contributions of around 1,100 words commenting on topical issues should be sent to [graeme.smith@pharmj.org.uk](mailto:graeme.smith@pharmj.org.uk) for consideration

■ SAFETY

## Interactions with other substances

From Mr S. Howshall, MRPharmS

Patients, generally, do not regard substances they consume as capable of affecting their prescription medicines. I always ask patients about over-the-counter medicines, herbs, vitamins and minerals when conducting medicines use reviews. Often, reluctantly, patients give this information with surprising results.

Last week I conducted an MUR with a patient chosen because she was on warfarin and had just been prescribed omeprazole. I intended to warn her to get a blood test because of the interaction of these drugs. I noticed that she had recently been prescribed two other proton pump inhibitors. She told me that these had not worked so I recommended a change of time for taking the drug. We went through the other drugs she was taking again and I was able to suggest changes to optimise her treatment. At the end I asked if she was taking anything else; she said paracetamol, for pain in her arthritic hands. We discussed that she should not take fish oil because of warfarin but she said that, on the doctor's advice, she was taking 1.5g glucosamine daily. I explained this was a high dose and could be the cause of her stomach problems. She is now going to stop taking the glucosamine but if I had not asked the extra questions it would not have come to light.

This is not the first time I have uncovered a potentially dangerous interaction of prescribed and purchased drugs. Pharmacists conducting MURs should always be on the lookout for such cases. Incidentally, I have recently learnt that one litre of ice cream can affect warfarin levels.

**Sue Howshall**  
*Wimborne, Dorset*

## Madopar packaging confusing

From Mrs S. J. Carr, MRPharmS

I recently visited a patient with Parkinson's disease whose medicines regimen had been changed by his consultant. He now takes three different strengths of Madopar. He has, among others, two bottles of Madopar 125. One is labelled "Madopar 125" and the other "Madopar 100/25". To us they are the same thing but to a

non-pharmacist, the people who have to take these medicines, they are confusing.

Is there any logical reason that these are labelled differently? For whose benefit are they labelled differently? Parkinson's patients are usually on complicated regimens plus several other (non-Parkinson) medicines, and it is up to us to try to simplify and clarify things as far as possible. It would help us and the patients, enormously if the industry would take some responsibility in this respect and label medicines clearly, unambiguously and consistently.

**Sharon Carr**  
*Specialist Clinical Pharmacist  
Brent Rehab Service*

A REPRESENTATIVE from the corporate affairs department, Roche, responds: The UK carton and label carries the name "Madopar 100mg/25mg hard capsules". Some countries within the EU have different labelling requirements and therefore cartons and labels in those countries may be labelled "Madopar 125". In each case the labelling states specifically that the capsule contains 100mg levodopa and 25mg benserazide. It may be that the patient you refer to had a UK/IE Roche pack and a parallel import pack from another EU country, which does happen. Legally, the parallel importer must over-label the imported pack, which does not appear to have occurred in this particular case, and hence, the difference in the labelling of each pack.

■ RETENTION FEES

## A comparison with other professions

From Mr G. Diamond, MRPharmS

Under the Nursing and Midwifery Order 2001, the Nursing and Midwifery Council is required to consult with registrants and other relevant parties before varying any fees related to registration. Like the Royal Pharmaceutical Society it offers a direct debit system, but the NMC is prepared to offer monthly payments to its members. Its consultation paper was sent to all NMC registrants, professional bodies, trade unions, consumer groups and government health departments, and is available on the NMC website. NMC fees are spent on fitness to practise (45 per cent), maintaining the register (22 per cent), standards promotion and policy development (14 per cent),

communication and events (10 per cent) and governance (9 per cent).

A survey of the health professions showed the NMC retention fee was £80 per annum (0.4 per cent of salary), the General Optical Council's was £169 (0.7 per cent of salary), the General Medical Council's £290 (1.4 per cent of salary), the General Dental Council's £409 (1.3 per cent of salary) and the Society's £267 (1.2 per cent of salary). These salaries are based on starting level, so not truly representative but, nonetheless, an indicator for comparison. I think our fees are unnecessarily high and should be more in line with optometrists.

Also, unlike nurses, we are given little in the matter of discussion or choice with regard to setting the fee. Again, it is left to the chattering middle class of the Society's Council with its grace and favour attitude towards its members.

**Gerry Diamond**  
*Manchester*

■ THE SOCIETY

## Are we really in tune?

From Mr I. G. Simpson, FRPharmS

Singing from the same hymn sheet — but are we in tune and in time? Tom Moberly, Mandie Lavin, Christine Gray and Eileen Neilson have done an excellent job at seeking to persuade us that, in some respects, the Society and the Department of Health, as represented in the Foster review, are "singing from the same hymn sheet" (*PJ*, 19 August, p216). In the imaginative illustration accompanying the article, readers with good eyesight and an interest in church music may have identified one of the hymns as "All glory, laud and honour", to the tune St Theodolph. Recalling the percussion accompaniment to this tune, which I learnt over 45 years ago, I fear that the Society and the DoH may not be marching to the same drumbeat, and there might even be the occasional wrong note.

First of all, Foster alleges that the Society is out of step with other regulators and threatens to bring it into line by requiring separation of its regulatory and professional leadership functions. However, from the comments of the Society's Vice-President, Gerald Alexander, it would appear that the Society's response to this will be to persuade the DoH that the Society can continue with the two roles, and that adequate separation can be

achieved and demonstrated (*PJ*, 5 August, p173).

Secondly, I think that Foster is out of step with the Society, and indeed with reality, in failing to recognise that it is the Statutory Committee and not the Society's Council, which carries out the disciplinary function, a situation which will continue under the Section 60 Order. This being the case, there seems to be no good reason to require the professional members of Council to be appointed by Government rather than be elected by members.

So, returning to the musical analogy, we may well be singing from the same hymn sheet, but there are still some discrepancies in the beat and a few bars of discord. There is much orchestration and rehearsing to be done before the Society can deliver a performance in unison with its members, in harmony with the DoH, and in time with other regulators.

**Ian Simpson**  
*Old Marston, Oxford*

## Ethics' guide for everyone

From Ms J. Landau, MRPharmS

To David Thomas, who thinks that non-practising pharmacists should not receive the "Medicines, ethics and practice guide" (*PJ*, 12 August, p188), I say that, although I am now non-practising, I am fortunately neither disinterested nor dead. As a paying member since 1960, I have been a life-long learner, maintaining an active membership and reading the *PJ* while in practice overseas. Even though many matters under discussion have not always concerned me directly, I have been interested in what has happened to others. Colleagues still regard my opinion as worthwhile and thousands of students have been influenced by my teaching (and ethics) during my career as a pharmacy faculty member in the US. I was also one of the few who voted in the recent Society council election. Pharmacy practice has played a huge role in my life and still does. I had, in fact, just read much of the guide when I came across the letter from Mr Thomas. Forgive the blowing of my own trumpet but I am entitled to receive it.

**Janet Landau**  
*Associate Professor Emeritus,  
Pharmacy Practice  
Long Island University, New York*

## Correction

Colin Deeney's letter response (p274) contained an error. The third sentence of the fourth paragraph should have read: "Rightly or wrongly they have accepted the possibility that AHR increases with the S-enantiomer alone and are looking at using the R-enantiomer alone clinically."