Asthma severity and adequacy of management

Sir—The report by Sergio Salmeron and colleagues (Aug 25, p 629)[1] raises many questions about the usefulness of guidelines for the management of acute asthma. It was reassuring, however, to see that only a few (0·3%) patients were given intravenous aminophylline.

There has never been any good evidence to support the use of aminophylline in acute asthma when β2 agonists are available,[2] but, inexplicably, this agent is widely prescribed in the UK and is recommended in the current UK asthma guidelines.[3] It is crucial that guidelines are based on sound evidence if clinicians are to be expected to follow them. The unfortunate difficulty of peculiar historical practices affecting national guidelines is surely a strong argument for adopting international evidence-based guidelines, such as those drawn up by the Global Initiative on Asthma.[4]

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1 Salmeron S, Liard R, Elkharrat D, Muir J-F, Neukirch F, Allrodt A, for the Asthme-Urgences (ASUR) study group. Asthma severity and adequacy of management in accident and emergency departments in France: a prospective study. *Lancet* 2001; **358:** 629–35.
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Sir—We note, from Sergio Salmeron and colleagues' report[1] a striking contrast between France and Japan in the severity of asthma in patients who visit accident and emergency departments.

Almost 75% of the patients were diagnosed as having severe and life-threatening asthma in the accident and emergency departments in their study, whereas more than 90% of patients in Japan are classified as mild to moderate[2] by use of similar guidelines based on peak flow, hypoxia, and responses to treatment. Since differences between the French and Japanese studies are too great to be explained by the small differences in guidelines, emergency systems, and genetic backgrounds that cause asthma, other factors should be considered.

We suspect that the differences arise, at least partly, from differences in the use of methylxanthine derivatives such as theophylline and aminophylline. Among the patients regularly treated for asthma in Japan, more than 75% are prescribed theophylline,[2] compared with 10% of asthma patients in France.[1] In addition, the use of aminophylline is recommended for moderate to severe asthma exacerbations in the Japanese guidelines[2] but not in guidelines of western countries.[1]

Patients with more severe asthma frequently underestimate their disorder because of a blunted perception of dyspnoea.[3] The alteration of perception is thought to be related to an impaired hypoxic ventilatory response and dysfunction of the carotid body. Methylxanthine, which is a respiratory stimulant that acts on the carotid body, resulting in stimulation of the hypoxic ventilatory response,[4] might recruit such blunted perception in patients with more severe asthma. Therefore, the use of theophylline may partly explain why Japanese patients seek care earlier during an exacerbation of asthma and why fewer of them require intensive care. For the same reason, the use of aminophylline in accident and emergency departments in Japan might contribute to the prevention of under-treatment of patients.

Asthma treatment accounted for 0·53% of total medical costs in Japan in 1998, whereas it represented 1·01% in the USA in 1993,[5] where the level of methylxanthine use is similar to that of France. 43% of the cost for asthma treatment was associated with acute care.[5] The relatively lower cost for asthma in Japan despite a similar prevalence could be related to the more extensive use of methylxanthines. Because of increasing medical costs for asthma, western countries may have to reconsider methylxanthines as cost-effective agents.

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Economics of surgery

Sir—J E Brazier and A G Johnson (Sept 29, p 1077)[1] address the key question about who should be treated with gallstones, and when and how?

Gallbladder stones present in one of three clinical stages: symptomless, symptomatic, and with complications. Gallstone complications, which include acute cholecystitis, common bile duct stones, with or without cholangitis or pancreatitis, gallstone ileus, and gallbladder cancer, are all potentially life threatening and almost always merit prompt treatment.

Most patients with symptomatic gallstones are candidates for laparoscopic cholecystectomy,[2] although sometimes the gallstone symptoms are difficult to differentiate from that of dyspepsia. Biliary pain can occur in about a third of the gallstone patients.[3] The delay of surgical treatment is associated with complications.

Insufficient data are available to assess whether prophylactic treatment is indicated in certain other groups with symptomless gallstones, such as patients with sickle cell disease and children, who may present diagnostic dilemmas, transplantation candidates and immunosuppressed patients who may have greatly increased morbidity and mortality from gallstone complications, and those who are isolated from medical care for long durations.[2]

The prevalence of gallstone disease is still increasing—currently up to 35%—and is higher in more-developed than in less-developed countries, and in certain ethnic groups.

Laparoscopic cholecystectomy is accepted and used worldwide. In 1997, 79% of cholecystectomies were undertaken laparoscopically in England and Wales.[4] The benefits from laparoscopic operations are not only cosmetic, but relief of pain and symptoms occurs earlier, the stay in hospital is shorter, and there are fewer postoperative hernia formations and wound healing and intestinal difficulties.

Laparoscopic surgery carries the risk of serious bile-duct damage, although there is a good evidence that, the incidence of biliary injury can be reduced to a rate comparable to that of open cholecystectomy.[5] Oral bile-acid dissolution therapy, contact solvent dissolution, or mechanical extraction through a catheter placed into the gallbladder (percutaneously or endoscopically), and fragmentation by shock-wave lithotripsy combined with bile-acid dissolution therapy have been developed and used in selected populations of patients. After lithotripsy, stones cleared in up to 95% of symptomatic patients with solitary non-calcified gallstones less than 20 mm in diameter in a functioning gallbladder. For patients with 20–30 mm gallstones and those with up to three stones in a functioning gallbladder, stone clearance rates are about 60%. An estimated 16% of all patients with symptomatic gallstones would fall into one of the above categories.[2]

According to Brazier and Johnson, cholecystectomy at today's price (UK£995) costs more than the surgeon's fee for a laparoscopic cholecystectomy with operative cholangiogram (£782), which costs more than mini-cholecystectomy (£548); the mini-cholecystectomy costs about the same as litotripsy without bile-salt treatment. To compare these data sometimes makes no sense. To be cost effective, the surgeon must know how much money will be spent with each procedure chosen. Cost data are largely unavailable because costs are difficult to estimate and charge data are jealously guarded. In addition, costs are not the same at different hospitals and, therefore, cannot be compared.

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Bayesian stopping rules for trials

Sir—Mahesh Parmar and colleagues, in their report (Aug 4, p 375)[1] on Bayesian approaches to monitoring randomised trials, raise several ethical and scientific questions.

They suggest that the continuous hyperfractionated accelerated radiotherapy lung cancer trial[2] was not stopped early only because the data monitoring committee chose to use a Bayesian approach. However, they use a sceptical distribution to represent the prior beliefs; if they had used the distribution of the trial clinicians' own less-sceptical prior beliefs, for example, the trial might have been stopped early. The choice of an appropriately sceptical prior or a prior with sufficiently small variance (representing strongly held or immovable beliefs) is likely to result in any trial being guaranteed to continue for its full duration. Consequently, the continuation of that trial for the full duration says nothing about whether Bayesian trial monitoring is better than classic methods and says everything about the choice of prior.

Given the views expressed on clinical equivalence by the clinicians at the start of the lung cancer trial, an equivalence trial design[3] might have been more appropriate. Monitoring could have taken the form of checking whether the CI for the estimated treatment benefit lay wholly outside the range of clinical equivalence. With this appropriate frequentist approach, the trial would probably not have been stopped either.

What Parmar and colleagues are really advocating is the need to survey an appropriate group of decision makers, whom the trial is trying to influence, before the start of the trial, to establish the least clinically significant difference (for sample size calculations in a conventional trial), the range of clinical equivalence (in an equivalence trial), or the prior beliefs in a Bayesian trial.

We argue that this step is essential when there is no previous scientific evidence, and, hence, beliefs about effect sizes must be relied on to help design and monitor the trial. When there is prior evidence, a systematic review and meta-analysis leading to an estimated effect size and CI is the appropriate starting point for the trial. Data monitoring can take the form of updating the meta-analysis with the new trial data. Such a frequentist approach recognises that previous information should be incorporated in stopping decisions, has no arbitrariness about choice of prior, and conforms to the view that the primary aim of a scientific trial is to collect and update evidence. An important but secondary purpose is to change people's beliefs.

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Authors' reply

Sir—Jon Nicholl and Steve Goodacre raise claim that the continuation of the trial says nothing about whether Bayesian trial monitoring is better than classic methods, and says everything about the choice of the prior. Only within the Bayesian framework, however, can such prior opinions be explicitly taken into account, giving a clear source for the targeted difference for the trial and the rationale for the approach to monitoring. The classic frequentist approach might superficially look more objective, but this is largely because the inevitable subjective judgments on these vital issues have been obscured. Of course, this freedom to include prior judgments brings with it an accompanying responsibility to do a sensitivity analysis to a justified range of opinions, which we suggest should be demarcated by a carefully chosen enthusiastic and sceptical prior.[1]

Nicholl and Goodacre also suggest that the lung cancer trial should have been designed as an equivalence trial. The Bayesian approach treats difference and equivalence trials in one framework without needing to prespecify which is of interest. All that needs to be quoted, as we do in our report, is the probabilities of the effect lying in certain regions of interest.[1]

We agree with Nicholl and Goodacre that previous information and beliefs on the likely size of effect,