Letters

Prehospital parenteral penicillin for meningitis

Urgent review of treatment criteria is needed

Editor—Harnden et al highlight an interesting problem in the early management of meningococcal disease: although it seems intuitively obvious that prehospital antibiotic treatment should improve outcome, this is extremely difficult to demonstrate objectively.[1]

In theory, at least three possibilities exist for the effect of early treatment on outcome, two of which are discussed by Harnden et al.

Firstly, they postulate that antibiotic administration is beneficial but that confounding by severity makes this hard to detect.

Secondly, they explore (and reject as unlikely) the possibility that antibiotic administration worsens the outcome by precipitating the release of endotoxin.

We suggest a third possibility: that in most cases prehospital antibiotic administration has little or no effect on mortality because the traditional diagnostic criteria for meningococcal disease reflect a stage of pathogenesis at which the opportunity for treatment benefit has already passed.

Shock, meningism, and petechial rash are manifestations of the profound inflammatory response to endotoxin rather than direct effects of the meningococcus itself.[2] Antibiotic treatment at this late stage of disease could be of little benefit to the patient as it fails to address the principal mechanisms of morbidity and mortality operating at this point.

The same group of authors recently identified three early signs of meningococcal disease in children—leg pains, cold hands and feet, and abnormal skin colour—which are reliably reported by parents and are often present at the first consultation with a general practitioner.[3] In New Zealand, as in many countries including the United Kingdom, guidelines for general practitioners emphasise late signs of disease.[4]

If treatment criteria for meningococcal disease were widened to include these early signs, the likelihood of demonstrating—and more importantly, achieving—a beneficial effect from the use of prehospital antibiotics would be greater.

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Competing interests: None declared.

1 Harnden A, Ninis N, Thompson M, Perera R, Levin M, Mant D, et al. Parenteral penicillin for children with meningococcal disease before hospital admission: case-control study [with commentary by R Perera]. *BMJ* 2006;332:1295-8. (3 June.)
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Trial in children with suspected meningococcal disease would be useful

Editor—Harnden et al's study raises important questions about the role of prehospital parenteral penicillin in children with meningococcal disease.[1] Their paper and accompanying statistical comment have shown the potential importance of excluding patients who would never have been considered for treatment. However, their study design is likely to have excluded a group of children with suspected meningococcal disease who were given prehospital parenteral penicillin.

Public health guidelines recommend that general practitioners administer prehospital parenteral penicillin to patients with suspected meningococcal disease, though the guidelines do not make specific recommendations about the clinical criteria on which general practitioners should base their decision.[2] Recent research shows that clinical features other than haemorrhagic rash can be important in identifying meningococcal disease,[3] reinforcing how difficult clinical decisions can be when treating an acutely unwell child.

In contrast, the formal case definition for meningococcal disease is decided after consultation between hospital clinician, microbiologist, and consultant in meningococcal disease in public health medicine, usually hours or days after hospital admission.[2] According to the methods section in an earlier paper,[4] this appears to have been the starting point for Harnden et al's study. Not all children treated with prehospital antibiotics for suspected meningococcal disease would meet the formal case definition, partly because of incomplete application of microbiological tests. For example, when we conducted an audit of such cases notified to public health in our region between 2000 and 2001, only 18 out of 36 cases (50%) had undergone adequate microbiological testing to confirm meningococcal disease.

A randomised controlled trial of prehospital parenteral penicillin in children with suspected meningococcal disease would be a useful next step and would address concerns about confounding. However, as demonstrated above, the inclusion criteria for such a study would need to be considered carefully for the findings to be relevant to general practitioners making decisions about acutely ill children in the community.

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Life without COX 2 inhibitors

Risks and benefits are determined by dose and potency

Editor—The paper by Kearney et al on the risk of atherothrombosis with cyclo-oxygenase-2 (COX 2) inhibitors and traditional non-steroidal anti-inflammatory drugs

(NSAIDs) supports the data of Hippisley-Cox et al, who revised the gastrointestinal risks of these drugs.[1 2]

A clear picture is forming, that the risks and benefits are determined by doses and potencies more than by their selectivity to the cyclo-oxygenases, with the exception of low dose aspirin, which permanently inhibits its platelet function without affecting endothelial prostacyclin, producing the useful antithrombotic effect. But in higher doses, aspirin is also toxic.

Over 20 years ago a report from England showed that all NSAIDs could produce some deaths per million prescriptions.[3] The least potent, such as ibuprofen, had the lowest risk of death (1.5), the risk increasing with potency (naproxen 4.6, diclofenac 5.3, piroxicam 7.0, and indomethacin 7.1).

The cardiovascular risk of COX 2 inhibitors follows a similar pattern. The most potent, such as rofecoxib and valdecoxib, are already withdrawn from the market. The potency of etoricoxib is unknown, although it worsens hypertension. The least potent, such as celecoxib and lumiracoxib, show that the class effect is COX inhibitors in general.

The odds ratios for adverse effects depend on the end point (cardiovascular or gastrointestinal), the reference parameters, and the dose: rofecoxib (1.32 to 3.58, in 12 studies), valdecoxib (threefold, one study), diclofenac (1.55, one study), other NSAIDs (1.16 to 2.06, three studies), other COX 2 inhibitors (1.45, one study), naproxen (1.14 to 1.5, three studies), ibuprofen (1.09 to 1.24, two studies), celecoxib (0.43 to 1.26 in six studies, 1.25 in three), lumiracoxib (1.14, not significant, in one study).[4 5]

Patients show benefits in their suffering and quality of life but pay with an increased risk of other important aspects that could eventually shorten their lifespan. However, continuous pain or inflammation could also shorten their lifespan through the associated stress and cardiovascular or gastrointestinal pathophysiological adverse reactions to the disease mechanisms. Doctors must explain this to patients and let them decide.

Doctors should recommend the least potent, least toxic agents, such as acetaminophen, celecoxib, and ibuprofen, in the lowest dose, for the shortest time, as well as protecting against cardiovascular risk factors and gastrointestinal adverse effects.

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Opioids can be prescribed safely in osteoarthritis

Editor—In their editorial on life without COX 2 inhibitors Shaughnessy and Gordon give examples of drug and non-drug measures shown to be effective in osteoarthritis, but their discussion of opioids was not referenced.[1] The omission of studies supporting the use of opioids was surprising, particularly when references for the non-drug measures were included even when the effect sizes were small or the data limited by small numbers.

Two systematic reviews of opioids in chronic non-cancer pain report several papers showing efficacy of opioids (morphine and oxycodone) in osteoarthritis, with an average reduction in pain intensity of 30%, generally considered to be clinically meaningful.[2 3] While Kalso et al note the worries of addiction and drug diversion (presumably the reason they are referred to as "a last pharmacological resort" by Shaughnessy and Gordon) and caution that not all patients respond to opioids, Kalso noted in a *BMJ* editorial in 2005 that the British Pain Society has published recommendations for the appropriate use of opioids in persistent non-cancer pain. The guidelines offer a framework for the safe prescribing of opioids in conditions such as osteoarthritis.[4] A recent paper highlighted that a quarter of general practitioners sampled did not prescribe opioids for patients with persistent chronic pain, and that prescription patterns were influenced by the doctor's beliefs about the appropriateness of opioids in chronic pain, in spite of these guidelines.[5]

We are conducting a trial focusing on the acceptability to patients of opioids for osteoarthritis pain. In addition, one of us (CR) has recently completed a qualitative study examining the views of patients with cancer pain when offered morphine. Interestingly, the phrase most commonly used by them was "last resort," which meant that they delayed the use of drugs such as morphine for as long as possible, suffering from uncontrolled pain as a consequence. Given the prejudice of this editorial, perhaps we should not have been surprised that some of these patients seemed to be reflecting the views of their doctors.

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Competing interests: None declared.

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Should we lower cholesterol as much as possible?

Policy on high dose statins is startlingly absent

Editor—Ravnskov et al raise some important concerns about the safety of treating much of the adult population with high dose statins but do not review how effective this might be.[1] In January 2006 the National Institute for Health and Clinical Excellence (NICE) Technology Appraisal requested that the NHS in England and Wales provide statin treatment to all those with cardiovascular disease and to all with a 20% or more risk of a cardiovascular event in the next 10 years.[2] This guidance gives no clue about the intensity of treatment, what dose of statin should be used, or what cholesterol targets people should be treated to (if any).

The vacuum in this guidance leaves the updated Joint British Societies' guidelines to fill the hole.[3] Is this wise? Their targets when using lipid lowering treatment are to lower total cholesterol to less than 4 mmol/l or a 25% reduction, or LDL-cholesterol less than 2 mmol/l or a 30% reduction, whichever gets the person to the lowest absolute value. These guidelines are based on consensus, not evidence. What is apparent is that to achieve such targets for many will require high dose statin treatment.

Is there evidence? There is emerging evidence to show some additional benefit compared with standard dose treatment in high risk people with established coronary disease but at the expense of harm related to myopathy and liver disorder, as pointed out by Ranskov et al.[1] If more aggressive

treatment is applied to lower risk people, as recommended by the joint guidelines, there is a real worry that this potential for harm could exceed benefit. This worry is supported in the IDEAL study which compared simvastatin 20-40 mg daily with atorvastatin 80 mg daily in 8888 patients with a history of myocardial infarction.[4] The primary end point of major coronary event was not significantly reduced by atorvastatin 80 mg daily. The incidences of adverse events resulting in discontinuation and raised liver enzyme activities were significantly greater with atorvastatin.

Does this matter? Even putting aside concerns of safety, the costs of lipid regulating drugs in England was £600m over the past year, or 8% of the total primary care drug spend, the single most expensive prescribing area. The NHS is under immense financial pressure and the absence of detail from NICE on intensity of treatment suggests it is failing to do its job in giving guidance on cost effective interventions.

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Competing interests: None declared.

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Cholesterol is good?

Editor—As Ravnskov et al state,[1] any revision of targets needs to be evidence based and responsible, taking into account the risks and benefits of such a measure. However, some of the authors' assertions are unclear and potentially misleading.

They do not explain in what way lowering coenzyme Q10 is harmful. The study of Rundek et al, one of the few that measured Q10 values, did so in insufficient numbers of patients, and the authors still conclude significance despite failing to show anything statistically solid.[2]

In one of the largest studies to date, the heart protection study, no evidence was found for neuropsychiatric and pulmonary side effects above placebo level.[3] With regards to cancer, Ravnskov et al disregard recent evidence that statins seem to protect against several forms of cancer, not least colorectal cancer[4]; instead, they favour older evidence. The heart protection study had cancer incidence (including various subtypes) as an end point, and no increased cancer risk was found in that trial.[3]

With respect to the authors' competing interests, three of them dispute the very association between hypercholesterolaemia and heart disease. In familial hypercholesterolaemia, in which young adults with no other risk factors may develop accelerated atherosclerosis, the underlying biochemical abnormality is well known (defects in low density lipoprotein receptors), thus making the authors' hypothesis almost completely untenable.

That a large proportion of the population may require pharmacological prophylaxis for cardiovascular disease seems counterintuitive. However, dietary patterns have deteriorated, we are in the middle of an obesity epidemic, and dietary measures are generally insufficient to mitigate cardiovascular risk in both hypercholesterolaemia and obesity. With the benefits of statins documented in several large studies, why deny statin treatment on the basis of comparatively inconclusive evidence?

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Competing interests: None declared.

1 Ravnskov U, Rosche PJ, Sutter MC, Houston MC. Should we lower cholesterol as much as possible? *BMJ* 2006;332:1330-2. (3 June.)
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Suicidal behaviour and SSRIs: updated meta-analysis

Editor—Our meta-analysis on the risk of suicide from selective serotonin reuptake inhibitors (SSRIs) was published last year.[1] In the light of recently released data for paroxetine by its manufacturer, GlaxoSmith Kline,[2] we have updated our results.

In our original analysis we were unable to distinguish between occurrences of non-fatal self harm and suicidal thoughts for patients in paroxetine trials. Our main analysis of these events therefore excluded the paroxetine data; in a sensitivity analysis we divided the events equally between self harm and suicidal thoughts. The new data released by GlaxoSmithKline come from placebo controlled trials of paroxetine and combine data on completed suicides, attempted suicide, and preparatory acts towards imminent suicidal behaviour into a single category of "definitive suicidal behaviour." For consistency with our original article, we have used data on all indications, although GlaxoSmithKline has provided a full breakdown. In 57 trials, there were 50/8958 events in the paroxetine arm and 40/5953 in the placebo arm. The newly released data suggest the figures in relation to suicidal thoughts were 33/8958 for paroxetine and 25/5953 for placebo. There is no new information on completed suicides.

Our updated findings are similar to those published.

Using the same bayesian random effects meta-analysis as before, the odds ratio for non-fatal self harm in patients taking an SSRI compared with placebo is 1.21 (95% credible interval 0.87 to 1.83). For suicidal thoughts the odds ratio is 0.80 (0.49 to 1.30). The previous results were 1.57 (0.99 to 2.55) for self harm and 0.77 (0.37 to 1.55) for suicidal thoughts. The results suggest that the overall effect on non-fatal self harm is reduced compared with our previous estimate, and slightly increased for suicidal thoughts.

As before, this analysis is limited by the length of the trials and inconsistent collection of safety end points. More evidence is needed to reliably assess specific adverse effects of SSRIs in relation to their use in particular disorders such as the increased risk of self harm recently reported for paroxetine in major depressive disorder.[3]

Updated tables and figures are available on request.

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Competing interests: DG and DA were members of the MHRA's expert working group on the safety of SSRIs. They acted as independent advisers, receiving travel expenses and a small fee for meeting attendance and reading materials in preparation for the meeting. DA has spoken on the methods of adverse drugs reactions in HIV at a scientific meeting attended by several pharmaceutical companies, and sponsored by GlaxoSmithKline. An honorarium was paid to her department.

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Hydatidiform mole and medical management of miscarriage

Editor—Trinder et al suggest that expectant management may be particularly appropriate for cases of incomplete miscarriage and as an alternative management in early fetal death.[1] One possible cause of first trimester miscarriage is hydatidiform molar pregnancy, which is associated with a significantly increased risk of subsequent development of persistent gestational trophoblastic disease.

Only around 40% of hydatidiform moles are detected as molar on pre-evacuation ultrasound examination, most appearing to be incomplete or missed miscarriages by sonography alone.[2] Furthermore, after termination of pregnancy patients presenting with symptomatic persistent gestational trophoblastic disease, compared with those who have the diagnosis made histologically after evacuation, are significantly more likely to experience life threatening complications and to require additional surgical or chemotherapeutic interventions.[3]

Routine histopathological examination of evacuated products of conception after failure of early pregnancy remains the gold standard for detecting molar pregnancy. The proportion of cases in whom tissue is submitted for histopathological examination is likely to fall with the increasing use of expectant or medical management of miscarriage. Consequently, the diagnosis of molar pregnancy will be missed in a few cases managed this way, with an increased risk of such patients presenting clinically with advanced persistent trophoblastic disease.

Before the widespread routine application of medical or expectant management of miscarriage, more accurate methods of assessing the patient's risk for possible molar pregnancy at presentation are required. A combination of ultrasound examination and serum human chorionic gonadotrophin measurement at presentation may better stratify risk, but no such data are currently available. Patients who opt to undergo medical or expectant rather than surgical management of early pregnancy failure should be made aware of this issue, and a routine check of chorionic gonadotrophin concentration after conservative management of miscarriage should be further considered in such cases.

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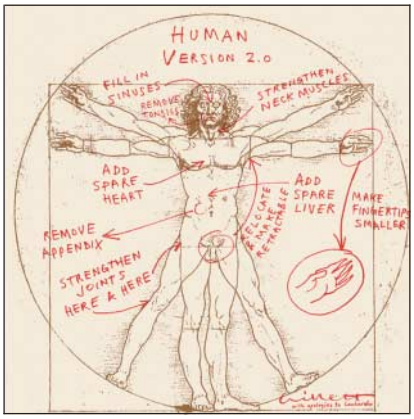
Postcripts to letter to God

Six fingers and testes tucked out of harm's way would be good

Editor—I offer a postscript to Brown's "Letter to God."[1]

If, God, you wish to make life simpler for man, perhaps any redesign could supply us with six fingers, rather than five on each hand. The logical consequence of this would be the development of a base 12 numeric system rather than base 10. Just think of the convenience—12 is exactly divisible by 2, 3, 4, and 6, whereas 10 is divisible only by 2 and 5. Those who have an extra digit due to polydactyly seem to cope very well.



It also seems a good idea to modify the testes so that they can produce sperm at a higher temperature and then perhaps you could safely tuck them out of harm's way inside the pelvic girdle? It has been many years since mine were last struck by a high speed projectile when playing sports, but I still vividly recall the intensity of pain which results from such impacts.

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1 Brown P. Letter to God. *BMJ* 2006;332:1341. (3 June.)

Some cosmetic changes would be helpful

Editor—I have some more requests to add to Brown's "Letter to God" to improve on the human body.[1]

God, when you fashioned us although Your intentions for creating body hair were noble, in the present climate neither men nor women desire it except for on the scalp. Perhaps You could increase the density of scalp hair at the expense of body hair? Although it is creating jobs for cosmetic surgeons and beauticians, body hair is unsightly therefore please could You create the new version of a human being without the body hair?

Perhaps You could avoid extreme skin colours and just give everybody a uniform but different shade of a suntan.

Some sort of robust framework (internal bra) for the breasts in women would be beneficial for management and organisation of mammary tissue.

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1 Brown P. Letter to God. *BMJ* 2006;332:1341. (3 June.)

Separating pipework for swallowing and breathing would be safer

Editor—Another sensible modification to add to Brown's requests to God would be the separation of the pipework for swallowing and breathing, greatly reducing the risk of choking and eliminating the risk of aspiration (thereby rendering the job of anaesthetists a lot less interesting).[1] That wasn't very intelligent design, was it?

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On why the eye lacks intelligent design

Editor—If the eye was designed, the designer is in need of urgent reappraisal.[1]

The eye is an organ of unsurpassed beauty, its evolution thought to be "absurd in the highest possible degree."[2] But it is hardly a perfect organ or represents perfect design. Its lens becomes cloudy, causing visual loss; its anterior chamber may be too narrow, predisposing to angle closure glaucoma. The vitreous detaches causing visual obscuration and predisposes to retinal detachments. The retina is back to front, prone to holes and tears. The blood supply of the retina and optic nerve is prone to occlusion or inflammation with resultant irreversible visual loss.

The nerve supply of the extraocular muscles also shows quite remarkable design flaws in their origin, pathways, and terminations. The optic pathways are hardly organised in a sensible fashion, indeed they may be affected by a stroke, resulting in visual loss with anatomically untouched eyes.

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Competing interests: None declared.

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