A PATIENT’S JOURNEY
Multiple sclerosis
Debbie Purdy,† Wendy Leedham‡

Debbie Purdy describes how she has been helped to embrace life with multiple sclerosis while campaigning to clarify the law on assisted suicide.

I first experienced my body refusing my directions in the summer of 1994. Less than half a mile from home my knees just wouldn’t hold me for another step, and I collapsed on the kerb. People going past probably thought I was drunk—a reaction I was to get used to. I went to my GP a couple of weeks later, because I was moving to Singapore and wanted reassurance that the collapse and a few other random experiences of unresponsive body parts were just a reflection of a more sedentary life since coming back to the UK from Hong Kong in 1990. I had spent five or six years abroad, experiencing life.

The GP didn’t even examine me—I made it pretty clear that I was returning to southeast Asia to solve the problems that my lifestyle change had created, and he went along with that.

I went to Singapore in September 1994 but returned to the UK several times in the following months for family funerals. That Christmas I saw a practice locum in Yorkshire who thought that my recent emotional turmoil was to blame for my odd symptoms (tiredness, some blurred vision, and wobbly walking) and referred me to a therapist. My dad’s doctor in Sussex thought I should see a neurologist and referred me to one in Brighton.

Both appointments came through for March 1995, so I went home first to Sussex to see the neurologist. He sent me straight for an MRI scan the following week. The technician was really thorough, explaining exactly what I should expect while I was in the MRI tube for about 45 minutes. The conveyer slid me in and, just a few minutes later, brought me out. The technician said I was done. I was in shock—what had they found? No one was able to tell me anything, that was up to the neurologist. My dad’s doctor in Sussex thought I was in shock—what had they found? No one was able to tell me anything, that was up to the neurologist. My dad’s doctor in Sussex thought I should see a neurologist and referred me to one in Brighton.

My appointment with the therapist in Yorkshire was coming up, so I called the neurologist and asked whether I should go to the appointment. He said “no” and asked me to come and see him before his surgery next day. “When I first saw you, I thought you had MS.” I waited for the other shoe to drop... “It is MS.” Most people who know me would find it pretty hard to imagine me speechless, but for about 48 hours I was.

Before I went back to Singapore I asked if I could scuba dive. “I don’t know, can you?” I think that set the tone for my ability to deal with MS. The diagnosing neurologist did not act like my life was over, so I certainly wasn’t going to. He told me he could not give me a prognosis other than to say that it wouldn’t get better so I should do whatever I wanted for as long as I could.

I thought that Omar, my new partner, would break up with me rather than deal with my diagnosis. My best friend was angry. “You wouldn’t abandon us because we got sick, why would we abandon you?” She made me realise it was self pity rather than MS that would drive people away. MS was now part of my life but didn’t have to define it, and other people’s problems were as real as ever.

I embarked on a journey of discovery, learning how to cope with each new symptom. I have had help and support from my friends and family and from an amazing group of people from every area of the medical profession and social services. But I think that, individually, they sometimes tended to act in isolation.

In particular the more senior medical professionals seemed to believe that they needed to find answers or solutions without reference to others, or even to me. They showed no lack of compassion; just too much responsibility and not enough time. I think that the culture of the NHS sometimes shows too much sympathy and not enough empathy. It is important for healthcare professionals to consider each patient as a person in a social context—for example, a partner may not always be the best person to help with self catheterisation or other intimate functions; in some cases their role as partner is more valuable than a role as carer.

I have been helped to embrace the disease for what it gives me, not just what it takes away. Quality of life is often judged to be lower by medical professionals than it is by the patient, because the able bodied see which of their abilities you don’t have, rather than what you have that maybe they don’t.

In the 14 years since my diagnoses of primary progressive MS, I have dealt with serious and substantial symptoms. I began to use a wheelchair occasionally in 1998 and by 2001 was unable to walk at all. In 2007 I could no longer propel my chair and began the process of getting an electric wheelchair.

This is one of a series of occasional articles by patients about their experiences that offer lessons to doctors. The BMJ welcomes contributions to the series. Please contact Peter Lapsley (plapsley@bmj.com) for guidance.
A DOCTOR’S PERSPECTIVE

The primary progressive form of multiple sclerosis, which affects around 15% of those with MS, can be more difficult than other forms to diagnose, as Debbie’s story illustrates. Instead of the relapsing-remitting pattern of symptoms seen in the much commoner form of MS, patients develop symptoms that are often subtle to begin with, which gradually worsen over time, although there may be long periods without any obvious deterioration. Many patients, like Debbie, first experience motor symptoms in the lower limbs. No disease modifying treatments are currently available for this type of MS, although a number of drugs are being investigated.

Several issues are raised by Debbie’s story. Communication between the different professionals involved in her care has not always been good, leading to delays in providing her with suitable solutions, such as her suprapubic catheter and colon irrigation system. As GPs we are used to communicating with secondary care professionals and other members of the primary care team, such as district nurses, but not always with other specialist nurses and advisors. Increasing use of shared electronic records may be one way to improve the management of patients with complex care needs.

Debbie is aware from discussions with partners in the practice that her GPs do not share her view on assisted suicide, but she says she feels able to trust us because of the relationship we have with her, based on honesty and communication. She feels that the trust patients have in their doctors is vital to good clinical care. Because of this trust she has felt able to discuss whether to take thyroxine for weight loss, and other issues concerning management of her symptoms. Discussing our personal views, when relevant and initiated by the patient, may encourage rather than hinder patients’ trust in us.

Debbie is clear that she would like to have the right to end her life when she chooses, with medical assistance, if her suffering becomes unbearable. I understand why she is fearful and why she wishes to be in control, but with all the expertise of medical care available I hope that she will always feel that her life is worth living, however disabled she becomes. Currently our role as doctors is not to end life but to work for solutions for suffering. To allow Debbie the choice to die would have huge implications for our society and our role as doctors—such as having to decide what constitutes unbearable suffering, and which of our patients who request to die should be allowed to die—implications I hope we will never have to face.

The lives of disabled people like Debbie are of immense worth; we need to value such people and help them to live lives that are as fulfilling as they can be. This requires medical, political, and financial commitment—as a GP I can only seek to do the best possible for my patient.

Wendy Leedham
wendy.leedham@bradford.nhs.uk

In 2000 I was taught intermittent self catheterisation but as my dexterity deteriorated that became impossible. I constantly turned down the idea of an indwelling catheter until a continence specialist caught me in bed with flu, unable to transfer to my chair and in floods of tears. In consternation she asked why I had rejected a suprapubic catheter. I told her that in all the years I had been talking to about catheters I had never heard of this one, but to please arrange it.

As a member of several patient groups in Yorkshire, I shared this new knowledge with other physically disabled adults with long term care arrangements. Some had suprapubic catheters for years, and others, like me, set about getting them. I think the increased specialisation within the NHS can be great, but there is a distinct problem with professionals thinking something has been covered elsewhere.

My experience of dealing with my condition is often troubled by other peoples’ conviction that they know the best way for me to handle a situation. At the moment, for instance, I am losing strength quite rapidly, and, because my legs don’t hold my body and my arms are weaker, transferring between my bed, chair, and toilet is becoming a nightmare. A partial solution has been a personal colon irrigation system, which allows me to control bowel movement.

Since being in a wheelchair and in particular since using an electric chair, I have put on weight. Not too much, as I try to be careful, but losing weight would certainly make life easier and less stressful. I asked my GP to treat me with thyroxine, but she was not happy about this suggestion and asked me to try a few other options first. I started seeing a nutritionist and taking sibutramine. We decided against assisted suicide because the probable side effects would be too difficult to deal with.

I have spent months trying these other options, but while my mobility and strength are still deteriorating my weight remains fairly constant, and my need for painkillers has substantially increased, partly in relation to my weight. Had I begun to see a nutritionist as soon as my mobility was reduced we could have avoided this situation, but now I think we should be able to look at the situation as it is, weighing up the use of painkillers and mobility problems against the side effects of hyperthyroidism.

At a recent Darzi Fellowship workshop I was introduced to the term “co-production,” describing the involvement of patients in decisions about their own treatment. The aim is not to insist that the patient is always right, but to recognise that individuals’ opinions should be taken into account—what is best for one patient may not suit another’s lifestyle or personal beliefs.

This same desire to improve the quality of my life and make my own choices about what constitutes an acceptable quality of life has led me to campaign to ensure that assisted death is part of the support available to patients who are suffering unbearably. This choice should be a patient’s choice, initiated by a patient and requested consistently. It should never be considered as one of a doctor’s options. This decision is not one for a doctor to make, nor should doctors be compelled to participate.

In response to my campaign, the director of public prosecution for England and Wales recently issued guidelines spelling out the circumstances in which people assisting suicide might expect not to be prosecuted. I believe that more clarity is still needed—for example, what do people who have no close family and friends do? A proper framework still needs to be put in place. But this guidance for the first time considers patients’ decisions about their own lives in terms of prosecutorial policies, and if this alleviates fears about the future for even one person I think it is valuable.

USEFUL RESOURCES

MS Society (www.mssociety.org.uk)—the UK’s largest charity for people affected by multiple sclerosis, offering information and support to anyone affected by the disease.

National Multiple Sclerosis Society (www.nationalmssociety.org)—the largest MS organisation in the United States, with chapters in every state.

MS Australia (www.msausmaustralia.org.au)—works to eliminate multiple sclerosis through quality research and excellent service for people with multiple sclerosis and their carers.

Multiple Sclerosis Society of New Zealand (www.msnz.org.nz)—non-profit organisation providing support for people with MS, educating the public and health professionals, and funding research.
I think it is unrealistic for doctors to think that a change in the law will mean that more people will end their lives, because the suicide rate among people with non terminal conditions like MS is extremely high. I think that's because people are scared about what will happen in the future. If people can be saved from ending their lives early then surely this is something that doctors should support.

Patients should not be made to bear the unbearable because of someone else's code of ethics, the impotence of our politicians, poverty, or the preparedness of our medical professionals to shoulder too much responsibility. Such factors should never determine provision of end of life choices.

The only person who is in a position to choose between one set of problems and another is the patient, because they are the person experiencing the problems. They will need guidance and support, but each person experiences similar symptoms differently; what is acceptable to one person may be intolerable to another. I want a law that will allow me to ask for help to die if living becomes unbearable. I don't want to make this choice, and I certainly don't know when I would, even if I could. I just know that if it were a legal possibility, a safety net, I would just be able to get on with dealing with each new symptom and keeping my marriage healthy. I hope to live a long and happy life as a disabled woman with support and care from many sources who respect my ability to make choices for myself, even if they would make different ones for themselves.

Competing interests: None declared.

Accepted: 15 October 2009

**UNCERTAINTIES PAGE**

**Should more patients with acute ischaemic stroke receive thrombolytic treatment?**

Joanna M Wardlaw,1 Peter A G Sandercock,1 Veronica Murray2

In developed countries, stroke is the third most common cause of death and the most common cause of dependency in adults. Thrombolysis with recombinant tissue plasminogen activator (rt-PA) was licensed for use in highly selected patients within three hours of acute ischaemic stroke in the United States in 1996 on the basis of the National Institutes of Neurological Disorders and Stroke (NINDS) randomised controlled trial (n=624),1 which showed substantially lower combined rates of death or dependency with this treatment (140/1000 fewer) despite an excess of symptomatic intracranial haemorrhage (60/1000 more). The Cochrane review of all data from randomised trials of rt-PA and a meta-analysis of individual patient data agreed with these findings.2,3 In Europe, a conditional licence for use within three hours in highly selected patients was granted in 2002 on the basis of the NINDS trial plus data from two European randomised controlled trials (n=930).1,5

However, six years after European and 10 years after US licensing, fewer than 10% of eligible patients receive thrombolysis—1-7% in the US,6,7 3% in Canada,8 3% in Germany,9 and 3.3% in Sweden (www.riks-stroke.org)—and use of rt-PA varies greatly between European countries.10 Clinicians and managers are uncertain about how widely to use rt-PA in routine clinical practice.11 The fact that treatment licenses are based on data from fewer than 1000 randomised patients with narrow entry criteria, the substantial excess of symptomatic intracranial haemorrhage, plus the restricted licence conditions may worry many clinicians.

**What is the evidence of the uncertainty?**

In 2009, a systematic review of all randomised trials comparing thrombolysis with control (mostly placebo) in patients with acute ischaemic stroke analysed 26 trials of various thrombolytic drugs, 11 of which tested rt-PA up to six hours after stroke (n=3977) (figure).12 Compared with control, rt-PA given up to six hours after stroke increased the risk of symptomatic intracranial haemorrhage about threefold (odds ratio 3.28, 95% confidence interval 2.48 to 4.33; P=0.0001), non-significantly increased the risk of death at the end of follow-up (1.14, 0.95 to 1.38; P=0.16), and significantly reduced the proportion of patients with a poor outcome (death or dependence: 0.78, 0.68 to 0.88; P=0.0001). Significant heterogeneity existed between trials in the estimate of effect of rt-PA on poor outcome but not on symptomatic intracranial haemorrhage or death (table). Treatment within three hours resulted in a similar sized increase in symptomatic intracranial haemorrhage, with no clear effect on death, but a greater reduction in poor outcome. Treatment between three and six hours also seemed to be beneficial—the upper confidence interval at six hours was similar to the effect of treatment in a stroke unit.13 Restricting the analyses to within separate time strata (zero to three and three to six hours) removed the significant heterogeneity for the effect on poor functional outcome (table). The randomisation methods used caused some imbalances in prognostic variables (such as stroke severity) at baseline between the treatment groups, which may have influenced the apparent effect of rt-PA. However, aggregate data indicate that for every 1000 patients treated within six hours, about 60 will avoid a poor functional outcome (110/1000 if treated within three hours; table).

These findings are consistent with all the data on any thrombolytic drug versus control (fig 1), which showed that thrombolysis might be beneficial up to nine hours

1 Division of Clinical Neurosciences, University of Edinburgh, Western General Hospital, Edinburgh EH4 2XU
2 Division of Medicine, Danderyd Hospital, Karolinska Institute, SE-182 88 Stockholm, Sweden

Correspondence to: J M Wardlaw joanna.wardlaw@ed.ac.uk

Cite this as: BMJ 2009;339:b4584
doi: 10.1136/bmj.b4584
## Outcome for all trials of recombinant tissue plasminogen activator in acute ischaemic stroke (up to October 2008)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Time</th>
<th>0-6 hours</th>
<th>0-3 hours</th>
<th>3-6 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of patients (no of trials)</td>
<td>3977 (11)</td>
<td>930 (5)*</td>
<td>2674 (6)*</td>
<td></td>
</tr>
<tr>
<td>Symptomatic (including fatal) intracranial haemorrhage</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Odds ratio (95% CI)</td>
<td>3.28 (2.48 to 4.33)</td>
<td>4.28 (3.26 to 7.77)</td>
<td>2.69 (2.16 to 3.06)</td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>0.00001</td>
<td>0.00001</td>
<td>0.00001</td>
<td></td>
</tr>
<tr>
<td>Events/1000 (95% CI)</td>
<td>60 (50 to 80)</td>
<td>70 (40 to 100)</td>
<td>60 (50 to 80)</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Late death</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Odds ratio (95% CI)</td>
<td>1.14 (0.95 to 1.38)</td>
<td>1.00 (0.71 to 1.41)</td>
<td>1.25 (0.98 to 1.59)</td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>0.16</td>
<td>0.99</td>
<td>0.14</td>
<td></td>
</tr>
<tr>
<td>Events/1000 (95% CI)</td>
<td>10 (–10 to 40)</td>
<td>0 (–50 to 50)</td>
<td>20 (0 to 50)</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Poor outcome (death or dependency)†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Odds ratio (95% CI)</td>
<td>0.78 (0.68 to 0.88)</td>
<td>0.64 (0.5 to 0.83)</td>
<td>0.85 (0.73 to 0.99)</td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>0.0001</td>
<td>0.0008</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td>Events/1000 (95% CI)</td>
<td>–60 (–100 to –30)</td>
<td>–110 (–170 to –50)</td>
<td>–40 (–80 to –10)</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
</tbody>
</table>

*Data not available for time to treatment in three small trials—most of the 230 patients were likely to have been randomised in the 3–6-hour window.
†Death by end of follow-up, usually 90 days.
‡Death or dependency by the end of follow-up (definition according to modified Rankin scale score of 3–6).

Is ongoing research likely to provide relevant evidence? Unfortunately, the publication of large observational non-randomised registries does not provide reliable evidence on the risk-benefit balance in many key categories of patients. The most pressing need is for studies that will enable safe and optimally effective delivery of rt-PA to more patients of all ages, within three hours and beyond. The only relevant ongoing trial is the Third International Stroke Trial (IST-3) of intravenous rt-PA versus control up to six hours after ischaemic stroke (www.dcn.ed.ac.uk/ist3). With over 1800 patients recruited so far, it is already more than double the size of the largest existing trial and aims to recruit 3100 patients by mid-2011. It includes patients over 80 years (580 so far) and those with lacunar strokes (153 so far), thereby already increasing 10-fold and threefold the world evidence on rt-PA in these key subgroups. The median time to randomisation is four hours, and by including patients treated up to six hours, IST-3 will show whether the benefit extends to six hours, and if so, which patients benefit most. By including patients with previous stroke, who are on aspirin already, with radiological features of early ischaemic change, and leucoaraisis, and by minimising the randomisation on key prognostic variables, IST-3 will answer many unanswered questions (box) and help change practice. With 3100 patients, IST-3 could detect a 4.7% absolute difference in poor outcomes (close to the 4% difference seen in the systematic review; table); and with 6000 patients, with early infarct signs on computed tomography, a history of stroke in the past three months, diabetes, or high blood pressure were also included from the trials. Although not excluded from some previous trials, we have little randomised evidence on rt-PA in lacunar stroke, posterior circulation stroke, and patients on aspirin. Hence, reliable randomised evidence is needed to inform clinical decision making in many patients with acute ischaemic stroke (box).

Thirdly, the latest time for safe and effective treatment is unclear. Three hours may be too late for some, whereas treatment could be effective well beyond six hours in others. Although the Third European Cooperative Acute Stroke Study (ECASS 3)—a randomised controlled trial of rt-PA between three and 4.5 hours after stroke in 800 patients—increased confidence that treatment is effective beyond three hours, all patients had to meet the restrictive criteria imposed by the licensing authorities. Ischaemic stroke has many causes, dynamic pathophysiology, and variable severity, all of which affect the length of time that cerebral tissue is “rescuable” by reperfusion therapy and influence the risk-benefit balance. Post hoc analyses of two trials suggest that the benefit of thrombolysis varies with stroke severity, with severe strokes seeming to gain less benefit than mild to moderate ones. Patients with severe strokes reach hospital more quickly than those with mild strokes, further confounding the association between time and treatment effect. Thus we still know relatively little about how to predict which patients will benefit and which are at high risk of adverse events.

### Uncertainties about thrombolysis in acute ischaemic stroke

- What is the size of the reduction in death or dependency when treatment is given at different times after stroke onset?
- What is the latest time for worthwhile benefit, and could it be more than six hours?
- What is the effect on death?
- Is the current upper age limit for treatment of 80 years justified?
- What key clinical and radiological features identify patients most (or least) likely to benefit?
- Should antithrombotics (an antiplatelet or anticoagulant) be coadministered to reduce the risk of early reocclusion after initial successful reperfusion?
Study or subcategory | Treatment n/N | Control n/N | Peto odds ratio (95% CI) | Peto odds ratio (95% CI)
--- | --- | --- | --- | ---
**Intravenous urokinase v control**
Chinese UK 2003 | 127/317 | 61/148 | 0.95 (0.64 to 1.42) | 0.94 (0.64 to 1.42)
Subtotal (95% CI) | 317 | 148 |  |  
Total events: 127 (treatment), 61 (control)
Test for heterogeneity: not applicable
Test for overall effect: z=0.24, P=0.81

**Intravenous streptokinase v control**
MAST-E 1996 | 124/156 | 126/154 | 0.86 (0.49 to 1.51) |  
MIST-I 1995 | 97/157 | 106/156 | 0.76 (0.48 to 1.21) |  
ASK 1996 | 84/174 | 74/166 | 1.16 (0.76 to 1.78) |  
Morris 1995 | 6/10 | 5/10 | 1.47 (0.26 to 8.18) |  
Subtotal (95% CI) | 497 | 486 | 0.94 (0.72 to 1.24) |  
Total events: 311 (treatment), 311 (control)
Test for heterogeneity: not applicable
Test for overall effect: z=0.41, P=0.68

**Intravenous tissue plasminogen activator v control**
Mori 1992 | 11/79 | 10/12 | 0.32 (0.07 to 1.48) |  
NIHSS 1995 | 155/312 | 192/312 | 0.62 (0.45 to 0.85) |  
ECASS I 1996 | 171/313 | 185/307 | 0.79 (0.58 to 1.09) |  
ECASS II 1998 | 187/409 | 211/391 | 0.72 (0.55 to 0.93) |  
ECASS 1999 | 140/218 | 155/403 | 0.82 (0.61 to 1.07) |  
ATLANTIS A 2000 | 64/71 | 56/71 | 2.13 (0.95 to 5.82) |  
ATLANTIS B 1999 | 141/307 | 135/306 | 1.08 (0.78 to 1.48) |  
Wang | 29/67 | 26/33 | 0.24 (0.11 to 0.56) |  
EPITHET 2008 | 28/52 | 29/49 | 0.81 (0.37 to 1.76) |  
Subtotal (95% CI) | 1968 | 1884 | 0.78 (0.68 to 0.88) |  
Total events: 992 (treatment), 999 (control)
Test for heterogeneity: z=20.95, df=8, P=0.007, I²=61.8%
Test for overall effect: z=3.84, P<0.001

**Intravenous streptokinase + oral aspirin v oral aspirin**
MIST-I 1995 | 99/156 | 94/153 | 1.09 (0.69 to 1.73) |  
Subtotal (95% CI) | 156 | 153 | 1.09 (0.69 to 1.73) |  
Total events: 99 (treatment), 94 (control)
Test for heterogeneity: not applicable
Test for overall effect: z=0.37, P=0.71

**Intra-arterial pro-urokinase v intravenous heparin**
PROACT 1998 | 18/26 | 11/14 | 0.63 (0.15 to 2.66) |  
PROACT 2 1999 | 73/121 | 44/59 | 0.54 (0.28 to 1.03) |  
Subtotal (95% CI) | 147 | 73 | 0.55 (0.31 to 1.00) |  
Total events: 91 (treatment), 55 (control)
Test for heterogeneity: z=0.04, df=1, P=0.84, I²=0%
Test for overall effect: z=1.97, P=0.05

**Intra-arterial urokinase v control**
AUST | 4/8 | 7/8 | 0.19 (0.03 to 1.51) |  
MELT | 29/57 | 35/57 | 0.65 (0.31 to 1.37) |  
Subtotal (95% CI) | 65 | 65 | 0.57 (0.28 to 1.14) |  
Total events: 33 (treatment), 42 (control)
Test for heterogeneity: z=1.19, df=1, P=0.27, I²=16.2%
Test for overall effect: z=1.59, P=0.11

**Intravenous desmoteplase v control**
DEDAS | 13/29 | 5/8 | 0.50 (0.11 to 2.35) |  
DIAS | 46/75 | 21/27 | 0.49 (0.19 to 1.22) |  
DIAS-2 | 72/123 | 34/63 | 1.20 (0.65 to 2.22) |  
Subtotal (95% CI) | 227 | 98 | 0.85 (0.53 to 1.40) |  
Total events: 131 (treatment), 60 (control)
Test for heterogeneity: z=3.10, df=2, P=0.21, I²=35.5%
Test for overall effect: z=0.61, P=0.54

**Systematic review of all randomised trials comparing thrombolysis with control in patients with acute ischaemic stroke.**

Effect of any thrombolytic agent v control on death or dependency at the end of follow-up

**Recommendation for future research**
Population: patients who fall outside existing licence criteria and have no contraindication to recombinant tissue plasminogen activator (rt-PA), especially those over 80, with vascular disease, who reach hospital and can be treated within six hours

Intervention and comparison: intravenous rt-PA compared with control (no rt-PA)
Outcome: symptomatic intracranial haemorrhage and death within the first seven days of stroke; death or dependency at three months or later after stroke; quality of life

mostly treated three to six hours after onset, the trial could detect a 3% absolute difference in poor outcomes.

IST-3 does not preclude further exploratory trials, such as ones that test extended time windows using imaging based selection criteria or different drugs. However, these trials necessarily have restrictive entry criteria and a small sample size. Greater statistical power is needed to deal with the heterogeneity in patients’ characteristics, which may influence the effects of rt-PA and hence the risk-benefit ratio in individual patients.

**What should we do in the light of the uncertainty?**
The current approved use of rt-PA within three hours is based on evidence from about 930 randomised patients. For treatment within six hours, the randomised evidence (3977 patients) is heterogeneous and small. We need additional randomised evidence from large trials to provide more precise point estimates of key outcomes and inform treatment decisions in individual patients.

In the meantime, patients under 80 who reach hospital, meet strict existing licence criteria, have no contraindication to rt-PA, and can be treated within three hours should be treated within the licence. If the licence is extended to 4.5 hours, then similar patients could be treated up to that time. All other patients who reach hospital and could be treated at any time up to six hours, with no clear contraindication to rt-PA, should be considered for inclusion in a randomised trial, such as IST-3. Given that rt-PA works for stroke and has a licence, it is unfortunate that fewer than 10% of patients receive it and that we do not know who is at greatest risk of hazard and who has the most chance of benefit. Patients are entitled to have individual risk-benefit analyses for all therapeutic measures, not least for treatments with such huge potential benefit as rt-PA.

**Contributors:** JMW conceived the article, analysed the data, and drafted the paper with VM; all three authors interpreted the data, revised the manuscript critically, and approved the final version. Heather Goodare, lay member of the IST-3 steering committee, and Richard Lindley, co-chief investigator of IST-3, also read the manuscript and provided lay and scientific comments. JMW is guarantor.

**Funding:** JMW is part funded by the Scottish Funding Council through the SInAPSE Collaboration (Scottish Imaging Network, A Platform for Scientific Excellence, www.sinapse.ac.uk). VM is in part funded by the Swedish Heart-Lung Fund, AFA Insurances.

**Competing interests:** The authors are on the IST-3 trial steering committee.

**Provenance and peer review:** Not commissioned; externally peer reviewed.
Metformin associated lactic acidosis

Emma Fitzgerald, Stephen Mathieu, Andrew Ball

Dehydration in patients taking metformin can lead to metformin associated lactic acidosis, a potentially fatal condition.

Metformin, a dimethylbiguanide, is a widely used oral antihyperglycaemic drug used in the long term treatment of type 2 diabetes mellitus. More recently it has also been used to improve fertility and weight reduction in patients with polycystic ovary syndrome. Many large studies have shown that intensive glucose control with metformin in overweight patients with type 2 diabetes is associated with risk reductions of 32% (P=0.002) for any diabetes related end point, 42% (P=0.017) for diabetes related death, and 30% (P=0.011) for all cause mortality compared with diet alone.1 Furthermore, metformin reduces microvascular end points, and its degree of glycaemic control is similar to that sulphonylureas and insulin. Metformin is considered to be first line treatment in overweight patients with type 2 diabetes whose blood glucose is inadequately controlled by lifestyle interventions alone and should be considered as a first line glucose lowering treatment in non-overweight patients with type 2 diabetes because of its other beneficial effects.2 It may also be useful in overweight patients with type 1 diabetes.

A potential complication of metformin is the development of type B (non-hypoxic) lactic acidosis. Although metformin associated lactic acidosis is a rare condition, with an estimated prevalence of one to five cases per 100 000 population,3 it has a reported mortality of 30-50%.4 Prognosis seems to be unrelated to plasma metformin concentration or lactate level.5 We present a report on a patient with type 2 diabetes who was receiving long term treatment with metformin and developed severe metformin associated lactic acidosis after dehydration, which resulted in renal impairment and consequent accumulation of metformin. This case illustrates the importance of stopping metformin treatment during intercurrent illness, especially dehydration. It also raises the point that continuation of other potentially nephrotoxic drugs should be carefully considered in these circumstances.

Case report
A 49 year old woman with type 2 diabetes mellitus presented with a five day history of diarrhoea, vomiting, and lower abdominal pain after a “day case” general anaesthetic for manipulation of a frozen shoulder. She had not stopped taking her regular medications (metformin, losartan, bendroflumethiazide, and atenolol) and had started a postoperative course of non-steroidal anti-inflammatory drugs. She had presented to her general practitioner complaining of nausea and vomiting and was prescribed an antiemetic (prochlorperazine). That evening she presented to her general practitioner again, this time with acute dyspnoea secondary to pulmonary oedema, and she was referred to hospital.

On admission, she was severely hypoxic and hypertensive but was alert and oriented. Her blood results showed severe lactic acidosis (pH<6.8) and acute renal...

The venous and arterial blood test results in our patient

<table>
<thead>
<tr>
<th>Blood test</th>
<th>Day 0</th>
<th>Day 1</th>
<th>Day 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>White cell count (10⁹ x cells/l)</td>
<td>20.3</td>
<td>7.9</td>
<td>14.3</td>
</tr>
<tr>
<td>International normalised ratio</td>
<td>1.8</td>
<td>1.1</td>
<td>1.1</td>
</tr>
<tr>
<td>Urea (mmol/l)</td>
<td>35.0</td>
<td>21.2</td>
<td>7.8</td>
</tr>
<tr>
<td>Creatinine (µmol/l)</td>
<td>7.69</td>
<td>470</td>
<td>162</td>
</tr>
<tr>
<td>Acidity (pH)</td>
<td>6.8</td>
<td>7.18</td>
<td>7.43</td>
</tr>
<tr>
<td>Bicarbonate ion (mmol/l)</td>
<td>4</td>
<td>13.2</td>
<td>23.8</td>
</tr>
<tr>
<td>Base excess (mmol/l)</td>
<td>Unrecordable</td>
<td>12.8</td>
<td>0.3</td>
</tr>
<tr>
<td>Lactate (mmol/l)</td>
<td>17</td>
<td>7.6</td>
<td>2.0</td>
</tr>
<tr>
<td>Partial pressure of oxygen, kPa (fractional inspired oxygen, %)</td>
<td>8.0 (100)</td>
<td>16 (70)</td>
<td>28.4 (40)</td>
</tr>
<tr>
<td>Partial pressure of carbon dioxide, arterial (kPa)</td>
<td>2.0</td>
<td>4.8</td>
<td>5.1</td>
</tr>
</tbody>
</table>

The effects of metformin on lactate production, with the green boxes indicating the sites where metformin affects the metabolic pathway (see text for full explanation)

Failure (serum creatinine 769 µmol/l) (table). Chest radiography confirmed pulmonary oedema. Non-invasive ventilatory support and early goal directed treatment was instigated. She remained hypoxic despite continuous positive airway pressure and was intubated that evening. Haemofiltration was started within six hours of arrival. She had a diagnostic laparoscopy to exclude ischaemic bowel in view of her abdominal symptoms and severe lactic acidosis.

She responded to treatment, and within 48 hours of admission she was extubated and inotropic support was discontinued. She needed continuous haemofiltration for four days before being discharged for ongoing intermittent dialysis. One month after presentation to hospital she had returned to her normal function and was back at work.

We know of two other cases of women with type 2 diabetes who presented to us in a similar way with vague abdominal symptoms, vomiting, and dehydration and in whom metformin associated lactic acidosis was also diagnosed.

Discussion

The patient had symptoms of vomiting and dehydration that were severe enough for her to contact a general practitioner and be prescribed antiemetics. In addition, she was taking an angiotensin II receptor antagonist and a non-steroidal anti-inflammatory. In addition, the measurement of mixed venous oxygen saturation from the tip of the central line (central venous oxygen saturation) may help to exclude sepsis as a cause of a severe lactic acidosis. In sepsis, oxygen consumption is in excess of the oxygen delivery and therefore more oxygen is extracted from the blood as it passes through the capillary beds. Thus in sepsis the central venous oxygen saturation would have an abnormally low value (<75%).

Metformin is thought to act by increasing glucose transport into cells and by decreasing hepatic gluconeogenesis. It decreases the activity of pyruvate dehydrogenase and the transport of mitochondrial reducing agents, and thus enhances anaerobic metabolism even in the presence of adequate oxygen. The presence of reduced insulin or insulin resistance increases the production of precursors for the tricarboxylic acid (Krebs) cycle. Inhibition of pyruvate dehydrogenase then channels the conversion of pyruvate into lactate rather than the aerobic pathway. As the figure shows, coexisting sepsis will accelerate the formation of lactate. Metformin has a short half-life (6.2 hours), and so in normal circumstances it will not accumulate. However, if ingested in toxic doses or in situations of impaired renal elimination, lactic acidosis does occur even in the absence of tissue hypoxia or any other risk factors. Clearly, additional precipitants affecting the glomerular filtration rate, renal perfusion pressure, or general tissue perfusion will increase the propensity for developing lactic acidosis. This is reflected by the
current recommendations on contraindications and guidelines for withdrawing metformin (box). 2

Although liver failure will reduce the excretion of lactate, the results of liver function tests were normal in our patient (and in the two cases not reported here), and therefore impaired liver function could not be a cause for the accumulation of lactate. Serum metformin levels were not available locally for us to obtain definitive confirmation of the metformin toxicity; however, it may be possible to arrange these with the pharmaceutical manufacturer.

Conclusion
Metformin associated lactic acidosis is a severe and potentially fatal condition that can be easily avoided. Its prevention is imperative; and we emphasise the importance of discontinuing metformin and any potentially renal toxic medications, especially angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists, in any patient who is at risk of dehydration or of developing renal failure.

Once patients become unwell, recognition of metformin associated lactic acidosis requires a high index of suspicion as severe lactic acidosis may suggest that sepsis is overwhelming and likely to be untreatable. Rapid supportive treatment and removal of toxic levels of metformin by haemofiltration is paramount. Measurement of mixed central venous oxygen concentration may be helpful in excluding sepsis as a cause of lactic acidosis and may prevent unnecessary investigational surgery and confirm that continued aggressive supportive treatment is appropriate. Patients can survive prolonged severe acidosis for more than 12 hours without any long term consequences.

The guidelines for reducing or stopping the dose of metformin are well documented in patients with laboratory evidence of worsening renal function, in the presence of intercurrent illnesses causing tissue hypoxia, and when iodinated contrast agents are used (box). However, when a previously well patient presents with an apparently less important insult such as dehydration, the guidance is less clear. Although we do not advocate the withdrawal of metformin in all patients in this situation, a careful clinical evaluation of renal function (particularly with coexisting use of nephrotoxic agents) and early consideration for treatment adjustment may help to avoid the life threatening adverse events of metformin.

We suggest that all patients taking metformin (or indeed any nephrotoxic agent) should seek medical advice if they develop dehydration as a result of either an inadequate intake or prolonged (>24 hours) gastrointestinal disturbance. They should be assessed clinically for evidence of intravascular volume depletion together with urgent blood biochemistry tests. Although our patient (and the two cases not reported here) had a serum creatinine concentration <130 μmol/l and an estimated glomerular filtration rate of >45 ml/min/1.73 m² within the preceding year, these values had not been checked in the period after the acute illness and before admission to hospital.

A thorough review of all medications is essential (especially non-steroidal anti-inflammatory drugs, angiotensin converting enzyme inhibitors, and angiotensin II receptor antagonists). Careful consideration of temporarily omitting metformin and any nephrotoxic agents may significantly decrease the risk of worsening renal function and consequently decrease the risk of metformin associated lactic acidosis. Follow-up, perhaps by a community district nurse, to ensure that glycaemic control remains stable may be necessary. Although the absolute risk of continuing the metformin in such a situation is not clear, and the risk of developing metformin associated lactic acidosis is reportedly rare, it is associated with very high mortality.

We reported our patient’s case (and the other two cases not reported here) to the Committee on Safety of Medicine, and we suggest that dehydration be added to the list of relative contraindications to metformin therapy.

Contributors: All authors analysed and interpreted the data and drafted and revised the article.

Competing interests: None declared.

Provenance and peer review: Not commissioned; externally peer reviewed.

Patient consent obtained.


Accepted: 30 March 2009