drug every five years. Founded because the pharmaceutical industry had withdrawn from the malaria market, the venture funds research and will manage development and production under licence. Pharmaceutical companies have donated compounds that might be developed into useful drugs. These partnerships build on the experience of many established programmes and have been joined by the Global Alliance for Vaccines and Innovation, which has funds from Bill Gates and other sources, including industry, to deliver vaccines to poor children.

Perhaps because of some of these new partnerships, governments are also becoming more interested in this issue. President Clinton has made budget proposals that would substantially increase the United States's expenditure on the problem. He is proposing $50m (£31m) for the Global Alliance for Vaccines and Innovation; a large increase in research expenditure on malaria, tuberculosis, and AIDS; a $400m (£250m) increase in health funding to poor countries; and a $1bn (£625m) tax credit on sales of new vaccines for diseases that cause over a million deaths a year (the *BMJ*'s website has the full text of a memorandum from the Carmel meeting to the White House). This package may well pass through Congress, particularly now that four US pharmaceutical companies have agreed to donate $150m (£94m) worth of vaccines through the alliance.[3] The World Bank is proposing to create a permanent £1bn fund for vaccines, partly because it is so convinced that paying for vaccines is one of the best ways of relieving poverty. Tony Blair is personally interested in the problem, and Britain has put money into several of the partnerships. The European Union has talked rather than acted, but perhaps it will want to join the worldwide initiatives.

Public-private partnerships may not solve the so far intractable problem of getting vaccines and drugs to the world's poor—and politicians may lose interest. On the other hand, the combination of good ideas on what to do and commitment to do something might mean that millions of unnecessary deaths and much suffering in the poor world could be prevented.

Richard Smith *editor BMJ*

1 Gwatkin DR, Guillot M. *The burden of disease among the global poor*. Washington, DC: World Bank, 1999.
2 Trouiller PT, Olliaro PL. Drug development output from 1975 to 1996: what proportion for tropical diseases? *Int J Infect Dis* 1999;3:61-3.
3 Ciment J. US drug companies announce vaccine initiative. *BMJ* 2000; 320:736.

Managing status epilepticus

New drug offers real advantages

Status epilepticus is a medical emergency familiar to accident and emergency departments, acute medical wards, and intensive care units. It is defined as a continuous seizure lasting for at least 30 minutes,[1] or two or more discrete seizures between which the patient does not recover consciousness, and in the 15-30 patients per 100 000 per year who present in status epilepticus mortality may be as high as 10%. The longer seizures persist the more difficult they are to control and the higher the mortality,[2] with an increase in neuronal damage and chronic epilepsy. Until recently phenytoin has been the drug of choice for managing prolonged seizures, but it has to be given intravenously and major side effects are common. Fosphenytoin is a prodrug of phenytoin, recently licensed in the United Kingdom, that seems to offer several advantages over its parent.

Status epilepticus is challenging to treat and may be difficult to diagnose. In early status epilepticus patients usually have visible tonic-clonic seizures, although motor-convulsive activity can decline. Diagnosis may require electroencephalographic monitoring, because some patients have seizure discharge without detectable motor activity. An electroencephalogram is also invaluable to exclude "pseudostatus epilepticus," which is seen more commonly in specialist neurological practice. Early treatment of status epilepticus means easier control, and basic life-support measures should not be ignored. Initial treatment of the patient should include the appropriate management of airway, breathing, and circulation and measurement of glucose and blood gases. Metabolic causes of seizures should be reversed as a priority. Emergency departments should have established protocols for dealing with this medical emergency.

If control of status epilepticus is delayed epileptic activity may outstrip metabolic capacity and glucose delivery, and metabolic and hypoxic-ischaemic brain and systemic injury may occur.[3] The seizures compromise cerebral vascular autoregulation, which in turn compromises hypothalamic autonomic regulation, and raised intracranial pressure may supervene. Complications such as cardiovascular collapse, arrhythmias, aspiration pneumonia, acute lung injury, and pulmonary hypertension may compromise cerebral oxygen delivery further. Metabolic derangement and cerebral and systemic acidosis with hyperpyrexia, rhabdomyolysis, and disseminated intravascular coagulation may cause multiple organ failure. Revealed seizures are then unusual.

Drug treatment divides into four stages[2]: that of premonitory, early, established, or refractory status epilepticus. Parenteral dosing with diazepam, lorazepam, or midazolam is preferred at the premonitory stage. Lorazepam is often preferred as it has a long duration of anticonvulsive effect and the best parenchymal distribution. Adverse events include a risk of respiratory arrest, hypotension, and impaired consciousness.[1]

Early management should include a prompt decision to use a long term parenteral anticonvulsant. Most patients in status epilepticus or who require a longer term anticonvulsant after acute presentation are treated with phenytoin. The pharmacology of phenytoin is complex but well understood. Given adequate

BMJ 2000;320:953–4

loading (18 mg/kg intravenously at 50 mg/min) and an adequate continuing dose, seizures are often successfully controlled. Phenytoin is effective when coadministered with diazepam in treating status epilepticus, controlling 60% to 80% of seizures.[4] Brain concentrations of phenytoin peak at 10 minutes and are three to four times those in plasma after injection. Phenytoin has a pH of 12, so intramuscular dosage is inappropriate. Local reactions to phenytoin occur often and thrombophlebitis necessitates frequent changes of cannulas and makes central administration the preferred route.

Fosphenytoin has been used for some years in the United States and can be administered intravenously or intramuscularly. Studies have found it to be as effective as phenytoin in treating status epilepticus, with several advantages over its parent drug. In one series of 81 patients with generalised convulsive status epilepticus treated with fosphenytoin 76 became seizure free.[5] Another showed that 37 of 40 patients treated with fosphenytoin were seizure free within 30 minutes.[6] Intravenous fosphenytoin is tolerated at infusion rates up to three times faster than those for phenytoin, and therapeutic concentrations are established within 10 minutes.[7–10]

Intramuscular administration of fosphenytoin has benefits: rapid and complete absorption, no requirement for cardiac monitoring, and a low incidence of side effects.[11 12] Patients with neurological or neurosurgical disorders which affect conscious levels, or patients for which the gastrointestinal route is not available, would be well suited to the use of intramuscular fosphenytoin. Side effects are similar to those of parenteral phenytoin: nystagmus, dizziness, pruritus, paraesthesias, headache, somnolence, and ataxia.[12]

Refractory status is characterised by seizure activity for about an hour in which the patient has not responded to therapy. General anaesthesia is recommended to abolish electroencephalographic and seizure activity and prevent further cerebral damage. Agents of choice for refractory status epilepticus are the newer agent propofol and older thiopentone, whose disadvantages include a tendency to accumulate in fatty tissues, an active metabolite, haemodynamic instability, long recovery time after infusion, and the need for blood concentration monitoring.

Continued seizure activity in status epilepticus is associated with neuronal damage. The aim should be to halt this activity urgently. The ideal drug should be 100% effective, administered quickly without compromising conscious level or producing cardiovascular or airway reflex effects, and have no harmful effects. For status epilepticus fosphenytoin is safe and effective in the emergency initiation and maintenance of anticonvulsant treatment and may usefully complement current practices for early control of seizures.

M T E Heafield *consultant neurologist*

Queen Elizabeth Hospital, Birmingham B15 2TH

MTEH has received a fee for speaking on status epilepticus and fosphenytoin at a study day organised by Parke Davis.

1 Lowenstein DH, Alldredge BK. Status epilepticus. *N Engl J Med* 1998;338: 970-6.
2 Shorvon S.D. Tonic-clonic status epilepticus. *J Neurol Neurosurg Psychiatry* 1993;56:125-34.
3 Shorvon SD. Emergency treatment of status epilepticus. In: Shorvon SD, ed. *Status epilepticus: its clinical features and treatment in children and adults.* Cambridge: Cambridge University Press, 1994:175-292.
4 Delgado-Escueta AV, Wasterlain LC, Treiman DM, Porter RJ. Current concepts in neurology: management of status epilepticus. *N Engl J Med* 1982;306:1337-40.
5 Knapp LE, Kugler AR. Clinical experience with fosphenytoin in adults: pharmacokinetics, safety, and efficacy. *J Child Neurol.* 1998;13 (suppl 1):S15-8; S30-2.
6 Allen FH Jr, Runge JW, Legarda S, Koup JR, Holmes GB, Hunt AJ, et al. Safety, tolerance and pharmacokinetics of intravenous fosphenytoin (Cerebyx) in status epilepticus. *Epilepsia* 1995;36(suppl 4):90.
7 Jamerson BD, Dukes GE, Brouwer KL, Donn KH, Messenheimer JA, Powell JR. Venous irritation related to intravenous administration of phenytoin versus fosphenytoin. *Pharmacotherapy* 1994;14:47-52.
8 Elson MA, Loewn GR, Voightman RE, Koup JR, Holmes GB, Hunt AJ, et al. Pharmacokinetics and tolerance of fosphenytoin and phenytoin administered intravenously to health subjects. *Can J Neurol Sci* 1993;20:S180.
9 Ramsay RE, Philbrook B, Fischer JH, Sloan FB, Allen FH, Runge JW, et al. Safety and pharmacokinetics of fosphenytoin (Cerebyx) compared with Dilantin following rapid intravenous administration. *Neurology* 1996;46: A245.
10 Ramsay RE, DeToldo J. Intravenous administration of fosphenytoin: options for the management of seizures. *Neurology* 1996;46 (Suppl 1): S17-9.
11 Ramsay RE, Wilder BJ, Uthman BM, Garnett WR, Pellock JM, Barkley GL, et al. Intramuscular fosphenytoin (Cerebyx) in patients requiring a loading dose of phenytoin. *Epilepsy Res* 1997;28:181-7.
12 Uthman BM, Wilder BJ, Ramsey RE. Intramuscular use of fosphenytoin: an overview. *Neurology* 1996; 46 (suppl 1):S24-8.

Practitioners of evidence based care

Not all clinicians need to appraise evidence from scratch but all need some skills

High quality health care implies practice that is consistent with the best evidence. An intuitively appealing way to achieve such evidence based practice is to train clinicians who can independently find, appraise, and apply the best evidence (whom we call evidence based practitioners). Indeed, we ourselves have advocated this approach.[1] Now, however, we want to highlight the limitations of this strategy and suggest two complementary alternatives.

The skills needed to provide an evidence based solution to a clinical dilemma include defining the problem; constructing and conducting an efficient search to locate the best evidence; critically appraising the evidence; and considering that evidence, and its implications, in the context of patients' circumstances and values. Attaining these skills requires intensive study and frequent, time consuming, application.

After a decade of unsystematic observation of an internal medicine residency programme committed to systematic training of evidence based practitioners,[1] we have concluded—consistent with predictions[2]—that not all trainees are interested in attaining an advanced level of evidence based medicine skills. Our trainees' responses mirror those of British general practitioners, who often use evidence based summaries generated by others (72%) and evidence based practice guidelines or protocols (84%) but who overwhelmingly (95%) believe that "learning the skills of evidence-based medicine" is not the most appropriate method for "moving … to evidence based medicine."[3]

BMJ 2000;320:954–5