

Aphasia in a farmer after viper bite

Sir—J M Polo and colleagues (June 22, p 2164)¹ report aphasia in a farmer after he was bitten on the left thumb by a viper. He developed swelling and ecchymosis of the corresponding limb. He reported to hospital within 2 h of being bitten, and his status was an absolute indication for immediate administration of polyvalent antivenom, according to WHO recommendations, to avoid the systemic effects of venom.² However, delayed administration of antivenom or waiting until he had systemic manifestations—ie, a 6 h wait—resulted in systemic envenoming.

We work in a rural area and have reported various poisonous snake bites.³ Between June, 2001, and May, 2002, six people were admitted to hospital for viper bite (four *Echis carinatus*, one Pit viper, one Russell's viper). The time lapse between bite and admission was 2.5, 1.0, 1.25, 4.5, 1.5, and 1.5 h, respectively. All patients brought the killed snakes to the hospital for identification.

Every patient developed progressive local oedema extending beyond the bitten segment of the limb, with ecchymosis. All were given polyvalent antivenom without test dose, preceded by subcutaneous adrenalin as prophylaxis against anaphylaxis to the antivenom.² Each patient recovered within 48 h without development of systemic manifestations.

A male farmer aged 32 years was bitten on the dorsum of his right hand by a Russell's viper while harvesting grass. He felt giddy and experienced severe pain at the site of the bite. Swelling developed rapidly with bleeding from the fang marks. He reported to hospital within 1.5 h. On arrival, his blood pressure was 80/60 mm Hg. He developed rapid progressive swelling with ecchymosis over the bitten limb, and enlarged tender lymph nodes in right axilla. His head was placed in a low position, intravenous crystalloid solution was administered, and 4 mL blood was drawn into a clean glass test tube for coagulation testing.² His blood did not clot for 20 min and remained incoagulable. We gave the patient ten vials of polyvalent antivenom in 200 mL dextrose over 60 min. Oedema lessened gradually over 48 h. His blood clotted within 10 min after 6 h of administration of antivenom. We gave him penicillin for wound infection and tetanus immunisation; he did not have diabetes.

Early administration of antivenom if the indication is clear² can

prevent development of venom-induced thrombus and subsequent development of disseminated intravascular coagulation.^{3,4} The delayed administration of antivenom to Polo and colleagues' patient resulted in systemic envenoming; the patient kept his head turned to the left, which suggests that he was pointing the lesion at left cerebral cortex.⁵ Timely administration of appropriate and adequate quantity of polyvalent antivenom is more beneficial^{2,3} than waiting.

*H S Bawaskar, P H Bawaskar

Bawaskar Hospital and Research Centre Mahad, Raigad, Maharashtra 402301, India (e-mail: himmatbawaskar@rediffmail.com)

- 1 Polo JM, Arcaya AV, Cid C, Berciano J. Aphasia in a farmer following viper bite. *Lancet* 2002; **359**: 2164.
- 2 Warrell DA. WHO/SEARO guidelines for the clinical management of snake bites in the southeast asian region. *Southeast Asian J Trop Med Public Health* 1999; **30** (suppl): 1–84.
- 3 Bawaskar HS, Bawaskar PH. Profile of snake bite envenoming in western Maharashtra, India. *Trans R Soc Trop Med Hyg* 2002; **96**: 79–84.
- 4 Cardoso JLC, Fan HW, Franca FOS, et al. Randomized comparative trial of three antivenoms in the treatment of envenoming by lance-headed viper (*Bothrops jararaca*) in São Paulo, Brazil. *Q J Med* 1993; **86**: 315–25.
- 5 Horton JC. Disorder of the eye. In: Brunald E, Fauci AS, Kasper DL, Hauser SL, Longo DL, Jameson JL, eds. *Harrison principles of internal medicine*; 15th edn. New York: McGraw-Hill, 2002: 164–77.

Drug resistance and influenza pandemics

Sir—Nikolaos Stilianakis and colleagues (May 25, p 1862)¹ discuss the issue of drug resistance and influenza pandemics.

They state that amantadine is associated with substantial toxic effects when used in the elderly and renally impaired. This belief is based on use of doses higher than those recommended in the UK, where the standard dose is 100 mg daily, and lower in the elderly and renally impaired. If elderly people receive half the daily dose of otherwise healthy adults, the nature and rate of side-effects are similar.² Side-effects associated with the standard UK dose are generally mild and transient.

The usefulness of amantadine for the control of influenza in residential homes is recognised in Canada, where outbreak-control protocols are in operation that detail the dose regimens for people with various levels of renal function.

Stilianakis and colleagues further state that amantadine at the lower dose of the

UK and Japan is not established as effective against pandemic strains of influenza A. Effective treatment is impossible to show for something that has not yet happened. However, all isolates of the H9N2 and H5N1 potential pandemic viruses that have been tested by the UK Public Health Laboratory Service have been susceptible to amantadine. Furthermore, whether neuraminidase inhibitors, at any dose, will be effective against such strains is unknown.

High levels of resistant virus have been isolated only when amantadine has been used for the management of influenza in closed communities such as residential homes. Surveys of isolates from the community have shown only low levels of resistance. In the UK, the Public Health Laboratory Service has been screening for resistant influenza A isolates held in their laboratories. In a preliminary report on around 1500 isolates, the frequency of resistance was 1.5%.³ The high level of resistance that is quoted when amantadine is used in closed communities might be biased. If amantadine successfully controls an influenza outbreak in such a facility, isolates will probably not be collected for characterisation. Even when resistant virus has been isolated in residential facilities, amantadine has a net positive benefit.⁴

Since amantadine was approved for treatment of influenza A in Japan in 1998, a third of individuals with symptomatic influenza during outbreaks are estimated to have been treated with amantadine. Despite this approval, no widespread circulation in the community of amantadine resistant viruses is reported.

It is incorrect to state that amantadine has not reduced the incidence of the secondary complications of influenza. Amantadine has lowered the incidence of such complications in individuals who are otherwise healthy, elderly, or at high risk. In combination with vaccination, amantadine used for treatment of outbreak control reduces the risk of secondary complications, including hospital admissions and death in the elderly. Treatment with amantadine has also lowered the rate of progression to pneumonia in immunocompromised patients in hospital.⁵

Any restrictions on the use of amantadine would therefore lessen its therapeutic value.

Peter Tooley

Alliance Pharmaceuticals Ltd, Avonbridge House, Chippenham, Wiltshire SN15 2BB, UK (e-mail: info@alliancepharma.co.uk)

- 1 Stilianakis NI, Perelson AS, Hayden FG. Drug resistance and influenza pandemics. *Lancet* 2002; **359**: 1863–64.

- 2 Petterson RF, Hellstrom PE, Penttinen K, et al. Evaluation of amantadine in the prophylaxis of influenza A (H1N1) virus infection: a controlled field trial among young adults and high-risk patients. *J Infect Dis* 1980; **142**: 377–83.
- 3 Elliot AJ, Zamboni MC. Amantadine susceptibility screening of influenza A isolates in the UK (1968–1999): 21st International Congress of Chemotherapy. Birmingham: International Society of Chemotherapy, 1999.
- 4 Mast EE, Hamon MW, Gravenstein S, et al. Emergence and possible transmission of amantadine-resistant viruses during nursing home outbreaks of influenza A (H3N2). *Am J Epidemiol* 1991; **134**: 988–97.
- 5 La Rosa AM, Malik S, Englund JA, et al. Influenza A in hospitalised adults with leukemia and hematopoietic stem cell transplant (HSCT) recipients: risk factors for progression to pneumonia. *Clin Infect Dis* 2001; **33**: 1160.

Author's reply

Sir—Amantadine doses of 100 mg daily are well tolerated in young adults, but 200-mg doses are frequently associated with adverse effects in the central nervous system. Furthermore, amantadine chemoprophylaxis with 100 mg daily is associated with frequent adverse events, including falls, in older nursing home residents.

In a retrospective cohort study, sequential dosing with 100 mg daily doses of amantadine (adjusted for renal insufficiency) was compared with rimantadine given for 24 or 28 days. Residents in nursing homes who received amantadine had around ten times higher rates of adverse events, including confusion and hallucinosis, and stopped medication early more frequently than when receiving rimantadine.¹

In studies of amantadine chemoprophylaxis with 200 mg daily during pandemic influenza, levels of protection against illness range from 30–100%, with an average of 60–70%.² These levels of protection are lower than those seen for disease occurring between pandemics. Although in one pandemic study, protection with 100 mg daily led to 49% reduction in illness compared with placebo, whether this dose would provide adequate prophylactic or therapeutic activity during pandemic influenza remains uncertain.

The neuraminidase inhibitors zanamivir and oseltamivir inhibit in vitro the H5N1 and H9N2 isolates from human beings, and all nine neuraminidase subtypes represented in avian species that might contribute to a potential pandemic strain. They are also active in animal H5N1 and H9N2 viruses.³ By contrast, the detection of de novo amantadine resistance in swine influenza A isolates, including those transmitted to human beings, and in a

small proportion of community isolates (in the absence of significant selective drug pressure) raises concern about the potential for resistance in a pandemic strain. Furthermore, up to 30% of treated people shed amantadine-resistant variants, the transmission of which cause infection and failure of chemoprophylaxis under close-contact conditions, such as in households and institutions. During the 1968 pandemic, in a family-based study of amantadine, in which treatment of ill index cases was combined with postexposure prophylaxis in contacts, illness was not reduced among contacts compared with placebo (6% efficacy compared to placebo).⁴

Amantadine chemoprophylaxis can prevent influenza A illness and by inference influenza-related sequelae. Several retrospective studies suggest that early amantadine treatment might lessen complication risk in selected populations. However, no data from prospective, randomised, controlled studies have yet established that amantadine treatment of acute influenza reduces the risk of complications, antibiotic use, or admission to hospital after influenza infection. By contrast, early treatment with neuraminidase inhibitors reduces the likelihood of lower-respiratory complications leading to antibiotic use.⁵

In the event of a pandemic, adequate availability of anti-influenza drugs could be assured only through stockpiling between pandemics. The choice of amantadine would be preferable to no drug. However, because of its narrower toxic-to-therapeutic ratio, requirement for individual dose adjustments, potential for resistance transmission, and uncertain effectiveness in reducing complications when used for treatment, it would be a less desirable choice for wide-scale pandemic use than alternative agents.²

F Hayden has been an investigator and paid consultant for Roche, GlaxoSmithKline, and other companies involved in development of investigational anti-influenza drugs (eg, R W Johnson, Biocryst, Abbot).

Frederick G Hayden

University of Virginia School of Medicine, Charlottesville, VA 22908, USA
(e-mail: fgh@hscmail.mcc.virginia.edu)

- 1 Keyser LA, Karl M, Nafziger AN, Bertino JS Jr. Comparison of central nervous system adverse effects of amantadine and rimantadine used as sequential prophylaxis of influenza A in elderly nursing home patients. *Arch Intern Med* 2000; **160**: 1485–88.
- 2 Hayden FG. Perspectives on antiviral use during pandemic influenza. *Philos Trans R Soc Lond B Biol Sci* 2001; **356**: 1877–84.
- 3 Govorkova EA, Leneva IA, Goloubeva OG, et al. Comparison of efficacies of RWJ-270201, zanamivir, and oseltamivir against H5N1, H9N2, and other avian influenza

viruses. *Antimicrob Agents Chemother* 2001; **45**: 2723–32.

- 4 Galbraith AW, Oxford JS, Schild GC, Watson GI. Study of 1-adamantanamine hydrochloride used prophylactically during the Hong Kong influenza epidemic in the family environment. *Bull World Health Organ* 1969; **41**: 677–82.
- 5 Kaiser L, Keene ON, Hammond J, et al. Impact of zanamivir on antibiotics use for respiratory events following acute influenza in adolescents and adults. *Arch Intern Med* 2000; **160**: 3234–40.

Lap burn due to laptop computer

Sir—The following story should be taken as a serious warning against use of a laptop computer in a literal sense. The patient, a previously healthy 50-year-old scientist and the father of two children, had been writing a report one evening in his home. Sitting comfortable in an armchair, he had placed his laptop computer on his lap while writing for about 1 h. The next day he noticed irritation and oedema of his penile prepuce. Furthermore, the ventral part of his scrotal skin had turned red, and there was a blister with a diameter of about 2 cm. These findings were verified when I saw the patient 1 day later. There were no signs of phimosis or balanitis. The patient recalled that, while sitting 2 days earlier with his computer on his lap, he occasionally had felt heat and a burning feeling on his lap and proximal thigh, a sensation that was relieved at least temporarily when the computer was moved slightly.

After the first 2 days, the penile and scrotal blisters broke and developed into infected wounds that caused extensive suppuration. More than a week later, the wounds were covered by dry crusts and thereafter were healing quite rapidly. No antibiotic treatment was needed.

When retrospectively checking the manual of the computer, the following safety instructions were found: “Do not allow your portable computer to operate with the base resting directly on exposed skin. With extended operation, heat can potentially build up in the base. Allowing sustained contact with the skin could cause discomfort or, eventually, a burn.” In the present case, however, the patient had lap burns although being dressed in trousers and underpants.

Claes-Goran Ostenson

Department of Molecular Medicine, Karolinska Institute, S-17176 Stockholm, Sweden
(e-mail: claes-goran.ostenson@ks.se)