Ocular timolol is a non-cardioselective adrenergic receptor antagonist of which variable amounts are absorbed by the nasal mucosa, producing unpredictable plasma concentrations. This variation in plasma concentrations is further affected by genetic subtype because oxidation of timolol shows genetic polymorphism of the debrisoquine type. Cardiopulmonary adverse effects of timolol remain the most common, and are usually reversible on its discontinuation. An alternative treatment for glaucoma should be selected in close liaison with ophthalmologists.

*Riona Mulcahy, Liesl Alcock,
Diammid O’Shea,

*Care of the Elderly and General Medicine, Royal Victoria Infirmary, Newcastle upon Tyne NE1 4LP, UK; and North Tyneside General Hospital, Rakeleane, North Shields


Cortical processing in persistent vegetative state

Sir—D K Menon and colleagues’ report (July 18, p 200) on cortical processing in persistent vegetative state could lead to confusion in the discussions on withholding or withdrawing treatment from patients in permanent vegetative state. For three reasons this report should not be considered in these discussions. First, these discussions deal with patients in the permanent vegetative state, which is different from the persistent vegetative state. Jennett and Plum5 defined persistent as sustained over time and permanent as irreversible. Persistent vegetative state is a diagnosis; permanent vegetative state is a prognosis.4 To avoid confusion between the terms persistent and permanent the Multi-Society Task Force on PVS has recommended that the term persistent vegetative state is not used. Rather, the term vegetative state should be used, and to add to this the duration: for instance vegetative state of 4 months’ duration. A patient in a vegetative state becomes permanently vegetative when the criteria of irreversibility are fulfilled. Second, the patient described by Menon et al was not in a vegetative state. This patient was able to recognise faces, for which visual fixation is required. Patients in a vegetative state do not fixate on a visual target.1 The diagnosis of vegetative state should not be made when there is doubt about the presence of visual fixation.7 Third, this patient was unlikely to be in a vegetative state since this diagnosis is usually made in patients with head trauma or hypoxic ischaemic encephalopathy. The principal findings in these patients is extensive multifocal or diffuse laminar neuronal loss. The white matter disease acute disseminated encephalomyelitis, the diagnosis of the patient described by Menon and colleagues, is not mentioned in a list of the most common disorders that have been reported to cause a vegetative state.3

J F Meilof
Department of Neurology H2-222, Academic Medical Centre, 1105 AZ Amsterdam, Netherlands (e-mail: j.f.meilof@amc.uva.nl)


Authors’ reply

Sir—J F Meilof makes several important points about persistent vegetative state. We agree that it would be unwise to use our data as the basis for making decisions about withholding or withdrawing treatment in such patients, but point out that we did not make such a suggestion. We did state that it was “difficult to make judgments about awareness or consciousness on the basis of these results”. We did, however, imply that the data provided an insight into the level of cortical processing of visual stimuli in persistent vegetative state, and believe that carefully conducted activation studies in such patients will provide important information about its pathophysiology. Such understanding may improve management.

We do not disagree with Meilof’s definitions of persistent and permanent vegetative state. Our patient was not in a permanent vegetative state, and we made no suggestion that this was the case. Although the Royal College of Physicians working group did suggest that the use of the phrase persistent vegetative state should be replaced by continuing vegetative state for patients who remained in this state after 4 weeks,1 this change in usage is by no means universally accepted. The Multi-Society Task Force on PVS in the USA which Meilof cites (inappropriately) clearly endorses the use of the term persistent vegetative state: “We define persistent vegetative state as a vegetative state lasting more than 1 month after acute traumatic or non-traumatic or lasting for at least one month in patients with degenerative or metabolic disorders or developmental malformations”2. Further, the description of a vegetative state lasting beyond 1 month as persistent is one that remains in common use in publications from both sides of the Atlantic, including a recent review article in The Lancet.1

Contrary to Meilof’s implication, we did not state that the patient showed sustained fixation on faces. In the original version of our report (as submitted) we specifically stated that “The subject exhibited no consistent or explicitly make the point that “the vegetative state can result from any acute insult or chronic process which severely damages part or all of the
Amsterdam Duration of Antiretroviral Medication (ADAM) study

Sir—Monique Reijers and colleagues (July 18, p 185) present results from an experimental induction-maintenance approach to HIV-1 antiviral therapy and conclude that it is inadvisable to attempt such a strategy in daily practice. Although this is the third double-blind, randomised clinical trial of this type to meet with failure, it may simply provide further evidence of the shortcomings of its French and US predecessors, rather than proof that alternative approaches to an induction-maintenance model for treatment of HIV-1 are doomed to fail.

We have been intrigued by the prospect of including hydroxyurea—a well-tolerated cytostatic agent shown to potentiate the antiviral activity of nucleoside reverse-transcriptase inhibitors in vitro—as part of a maintenance therapy regimen. By suppressing T-cell proliferation, hydroxyurea might contribute in a bimodal fashion to the success of such a regimen by potentiating the preferential intracellular phosphorylation of nucleoside (and nucleotide) agents, while at the same time limiting the availability of new target cells.\(^1\)

We report a chronically infected patient (HIV-1 seropositive since 1989) in our clinic who started antiretroviral therapy in October, 1996 (baseline plasma viral load 4·74 log\(_{10}\) copies/mL; CD4 T cell count 414 cells/μL) with a typical protease-inhibitor-containing triple regimen (stavudine, lamivudine, indinavir [indinavir was replaced with nelfinavir March, 1997] as standard doses). After 14 months on this triple regimen with a plasma viral load consistently less than 20 copies/mL (Immunodiagnostic Laboratories, San Francisco, CA, USA), he discontinued his triple combination and switched to the dual combination of didanosine (400 mg once daily) and hydroxyurea (500 mg twice daily). In preparation for the scale down of drugs, hydroxyurea was initially added as a fourth drug to the original triple combination 2 months before discontinuation of this induction regimen and the switch to didanosine plus hydroxyurea. During the 8 months on this maintenance regimen, his plasma viral load has been maintained between 200 and less than 20 copies/mL (figure). Whereas both Reijers and Havlir\(^2\) reported that rapid viral clearance rates during the induction phase were predictive of success during the maintenance therapy phase, our patient’s plasma HIV-1 RNA did not fall to less than 20 copies/mL until about 24 weeks after initiation of triple-combination therapy.

This is the only patient in our practice whose treatment course (on his request) has been managed in this way, and it is possible that—with his low plasma viral load at the time of triple-therapy induction—dual therapy with didanosine plus hydroxyurea may have itself resulted in sustained suppression of plasma virus to less than 20 copies/mL. Whether newly generated cellular immune responses to HIV-1 may be contributing to the sustained viral control in this individual is also being investigated. Clearly, until we can report on additional successes (or failures), no definitive conclusions can be made about the efficacy of this particular induction-maintenance approach. But as greater numbers of patients who have successfully endured the distresses associated with triple-combination therapy in the past 2–3 years begin to demand a reprieve from their drug-dictated existences, we believe the more manageable maintenance therapy regimen of once-daily didanosine and hydroxyurea may hold great promise. This regimen deserves rapid and thorough systematic investigation by both government and industry.

Ramón A Torres, Paul C Bellman, Mike Barr
Bently-Salic Medical Group, New York, NY; and Section of HIV Medicine, St Vincent’s Hospital, New York, NY 10011, USA (e-mail: mrbarr@earthlink.net)