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Aciclovir neurotoxicity is an important side effect of therapy in patients with renal impairment

Editor – We read with interest the article by Bell and colleagues (*Clin Med* June 2009 pp 231–5). They describe aciclovir therapy as essentially safe, highlighting the potential risk of crystal nephropathy. This potentially life-threatening complication is well recognised in nephrology, but not widely publicised, as it is often only evident in the presence of renal impairment. Recognition has implications for all physicians given the prevalence of chronic kidney disease and acute kidney injury. Such concerns might explain five patients not receiving full dose aciclovir in their study.

Aciclovir and latterly valaciclovir are established antiviral agents versus herpes simplex (HSV) and varicella zoster (VZV). Neurotoxic side effects have been described since the early 1980s.[1–3] Such cases often resulted from recommended aciclovir dosing for HSV encephalitis in the context of renal impairment. As approximately 90% of the drug is renally excreted; half-life and serum levels of aciclovir are markedly elevated in renal disease.

A range of symptoms from tremor to coma have been described, with typical onset 24 to 72 hours after both oral and intravenous aciclovir. Visual hallucinations and death delusion are striking features in patients prescribed aciclovir with previously normal brain function (usually for treatment of shingles or as anti-cytomegalovirus prophylaxis).[3] In patients with presumed encephalitis, failure to consider aciclovir neurotoxicity may lead to misinterpretation of neuropsychiatric symptoms as worsening encephalitis; precipitating inappropriate dose increases, rather than reduction or withdrawal.

The exact mechanism is unknown. 9-carboxymethoxymethylguanine (CMMG) is an aciclovir metabolite, present in serum and cerebral spinal fluid. In patients with neuropsychiatric side effects, significantly higher serum CMMG levels have been demonstrated; with stronger symptom correlation than aciclovir.[5] Most affected patients had renal impairment.[5]

To improve the therapeutic regimen aciclovir dosing should always be adjusted for renal function[6] and patients adequately hydrated prior to oral or intravenous administration. Possible aciclovir neurotoxicity should be considered with new neurological symptoms after 24 hours, particularly in the presence of renal impairment. Serum aciclovir measurements require 24 hours in most UK centres and often lag behind clinical signs. Levels might be useful for diagnostic confirmation. Early recognition with appropriate dose changes is crucial. If distinguishing worsening encephalitis from neurotoxicity proves difficult, a trial of haemodialysis might be appropriate.[7]

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Medicine at the sharp end

Editor – We read with interest the article by McNeill and colleagues (*Clin Med* June 2009 pp 214–8) suggesting that benefits from a consultant presence on an acute medical unit (AMU) included greater numbers of same-day discharges and a shorter length of stay. There remains little evidence as to why consultant presence results in these positive outcomes.

We retrospectively audited 145 randomly selected patients admitted via the AMU at the Countess of Chester Hospital NHS Foundation Trust. Patients clerked by a foundation or core medical training grade doctor were then reviewed on the post-take ward round (PTWR) by a consultant or middle grade (specialist registrar (SpR) or staff grade). We studied the number of same-day discharges following the PTWR and accuracy of diagnosis at the PTWR compared with final diagnosis on the hospital discharge summary.

Consultants reviewed 72 patients (mean age 68 years; 33 men) and middle grades reviewed 73 patients (mean age 66 years; 39 men) on the PTWR. Consultants made an accurate PTWR diagnosis in 69 patients (95.8%) which was significantly higher (χ^2, $p<0.0001$) than the middle grades who made an accurate diagnosis in 60 patients (82.2%). The main reason for this difference appeared to be that there was only a documented PTWR diagnosis in 89% of the patients reviewed by middle grades, whereas there was a written PTWR diagnosis in all (100%) of the patients reviewed by consultants. Consultants also discharged higher numbers of patients at the PTWR (17 patients *v* 6 patients; χ^2, $p<0.01$).

Our data confirm that consultant review at PTWR results in a greater number of same-day discharges and suggests that the benefits of a consultant presence on the AMU may be due to the higher rate of accurate initial diagnosis. This seems to be because of an increased willingness of consultants to commit to a written diagnosis. The Joint Royal Colleges of Physicians Training Board curriculum for general (internal) medicine identifies 'developing a problem list and action plan' as a key competency, and we would suggest that trainees should be encouraged to commit to and

'formulate admission diagnoses' as this may improve management of patients and facilitate earlier discharge.

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In response

The issues raised by Joseph and colleagues in response to our article are thought provoking. It appears likely that consultants are often more able than trainees in committing to a clear problem list and action plan. Reports by the National Confidential Enquiry into Patient Outcome and Death and the Royal College of Physicians highlight the dangers of trainee-led clinical decision making and also emphasise the importance of consultant review early in the acute admission.[1,2] Our study showed that for the acute medical unit (AMU) to be effective, the consultant decision-making process should not be restricted to the post-take ward round.

Our prospective study of 2,928 patients over an eight-month period demonstrated that early consultant-led review of patients admitted to the AMU significantly reduces length of stay when compared to the consultant-led post-take ward round model. It would therefore appear intuitive that improvement in patient care will only be achieved if there is continual consultant presence on the AMU throughout the working day and early evening. It is therefore imperative that trusts continue to expand acute medicine consultant numbers. In addition AMU consultant job planning must reflect the importance of a strong consultant presence at the AMU front door.

The additional issue raised by Joseph and colleagues of how to develop acute medicine trainees in to consultant decision makers is pertinent. Our study adds weight to the evidence that acute medical services should be consultant led.[1,2] Within this setting, the need to allow registrars to develop decision-making skills must be balanced against the need to provide effective service provision and good clinical governance. Further study to elucidate the most effective educational strategies to deliver the acute medicine syllabus is required.

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An urgent access neurovascular clinic

Editor – We very much enjoyed reading the informative paper by Briley, Durkin and Meagher highlighting problems in gaining access to neurovascular clinics (*Clin Med* June 2009 pp 236–8). There is no doubt that the evaluation of high-risk transient ischaemic attack or minor stroke patients remains a key priority, and that investigation within the outpatient setting adds to the delay in treatment.

We have noted a large increase in the number of patients presenting with focal neurology which we believe is in part due to the national FAST campaign raising public awareness. There is reasonable evidence suggesting benefit from carotid endarterectomy in the early period after ipsilateral ischaemic hemispheric event.[1] This has led us to introduce a system whereby such high-risk patients are offered same-day carotid duplex imaging during working hours.

The referral for carotid duplex is no longer dominated by neurology teams, but additionally comes from a variety of specialties, including the emergency department. This minimises delay in investigation and allows the delivery of definitive treatment more quickly to the subgroup of individuals shown to have a responsible carotid stenosis. The revision of our policy has proved to be effective, identifying candidates requiring carotid intervention earlier, hence improving outcome.[1]

After considering Briley *et al's* proposed solutions, we believe having daily open-access clinics to ensure evaluation within 14 days remains inferior to that of direct in-hospital assessment as the issue of time delay introduced by outpatient management remains.[2] Adapting the mechanisms for the referral and undertaking of in-hospital carotid duplex scanning may limit the costs associated with inpatient stay and minimise the delays seen in the outpatient setting.[1] Such an approach, we believe, can be widely applied and should also be considered as part of the possible solution.

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