

# MATTERS ARISING

## What is the relevance of the endothelins in subarachnoid haemorrhage?

In their interesting study of endothelins in subarachnoid haemorrhage (SAH), Gaetani *et al*<sup>1</sup> claimed that "Cisternal levels of endothelin-1 and endothelin-3 are not directly related to the occurrence of arterial vasospasm... or to other major clinical patterns of SAH". This conclusion is justified by their results in 55 patients with endothelin values from cisternal CSF, especially by only six values of both endothelins higher than the mean (SD). These results are in accordance with some recently published data.<sup>2,3</sup> We found no increase in big-endothelin, the active precursor of endothelin-1, in plasma and CSF from non-operated patients with aneurysmal SAH.<sup>2</sup>

The strong vasoconstrictive potential of the endothelins, discovered in 1988, made these peptides likely candidates in the search for a cause of the vasospasm in subarachnoid haemorrhage (see review by Greenberg *et al*<sup>3</sup>). First clinical reports in 1990<sup>3</sup> seemed to confirm their importance in patients after subarachnoid haemorrhage, but most studies were done in operated patients or small patient groups. Thus the study by Gaetani *et al*<sup>1</sup> is very important as the patient number is adequate and the CSF was withdrawn before surgical clipping of the aneurysm.

Unfortunately the authors tried to change the interpretation of their results in summarising: "...ET may potentiate, or may be potentiated by, other factors playing a consistent pathophysiological role in the development of vasospasm". But the most important point of this study seems to be the lack of any clinical correlation between the endothelins and the major complications in SAH. The speculation about a role of endothelins in relation to subarachnoid blood clots or leukotrienes highlights the well known problem that the search for a single causal factor of the vasospasm after SAH is always disappointing<sup>2,3</sup> and a complex multifactorial aetiology of vasospasm is most probable.

The reasons for the difference between the studies with negative results for the endothelins<sup>1,2</sup> and with increases<sup>3</sup> are various and only partly mentioned by Gaetani *et al*.<sup>1</sup> The importance of surgical stress is clearly considered by Gaetani *et al*,<sup>1</sup> but besides this, a more general stress reaction is possible, which is dependent on the severity of the disease. This is supported by the results in myocardial infarction<sup>4</sup> in which endothelin activation is related to the severity of the infarction. A further important point is the development of ischaemic damage after vasospasm. An activation of the endothelin system is described in ischaemic stroke, especially after more severe infarction.<sup>5,6</sup> Thus increased endothelins after SAH may more closely reflect the result of the vasospasm—namely, the vascular and tissue damage—than the

cause. The patients of Gaetani *et al*<sup>1</sup> were in good clinical condition (Hunt and Hess I-III) with probably no or minor ischaemic damage. Therefore this study cannot contribute to the question of the relation of the endothelins to the vascular and cerebral damage after SAH.

To answer the title question whether endothelins are relevant in patients after SAH, the interpretation of Gaetani *et al*<sup>1</sup> and of our own data<sup>2</sup> does not support the idea that endothelins have a major clinical role in SAH.

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### Parkinson's Disease

We read the excellent review by Marsden<sup>1</sup> with great interest. We are troubled by the cognitive impairment seen in patients with Parkinson's disease as it raises the question of the patient not being able to give informed consent. This leads to how valid is consent in this group of patients to some of the treatment strategies that are becoming available. We refer in particular to the use of clozapine, which may cause agranulocytosis, cardiac dysrhythmias, and postural hypotension. Clozapine is licensed in the United Kingdom solely for the treatment of resistant schizophrenia. The clozapine patient monitoring service is provided by Sandoz only for patients who have firstly been diagnosed as schizophrenic and secondly have been either unresponsive to or intolerant of previous neuroleptic treatment. This certainly limits the use of clozapine in routine practice. We do, however, agree with Marsden<sup>1</sup> that the rationale for use of this drug in parkinsonian patients with psychotic symptoms is justified and maybe in the years to come it will become available as a treatment option.

Risperidone, which is now licensed for treatment of schizophrenic patients in the United Kingdom, is a similar drug to clozapine and should be considered in the treatment of parkinsonian patients with psychotic symptoms.<sup>2</sup> This has the advan-

tage of not being subjected to regular blood monitoring as is the case with clozapine.

We also agree with Marsden<sup>1</sup> with regard to the use of electroconvulsive therapy in the treatment of parkinsonian patients with depression. This also raises the question of informed consent. We are limited in being able to use the powers of the Mental Health Act, as the patient would have to be placed on Section 3, after which we would have to get a second opinion approved doctor from the Mental Health Commission to review the management plan and to agree with electroconvulsive therapy as the most effective treatment option. The use of electroconvulsive therapy has certain emotive connotations, and it has also been subjected to a lot of media criticism; hence we have not been able to use it on a routine basis in the treatment of this group of patients.

We also wish to enquire whether Professor Marsden has any comments on the use of electroconvulsive therapy in parkinsonian patients who are at the end stage, with on/off symptoms. This treatment option is being recommended in the United States.<sup>3</sup>

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### Marsden replies:

Fitzgerald and Devakumar raise important points over the management of the patient with Parkinson's disease who is confused, or demented, or both. The issue of informed consent in such patients is not restricted to Parkinson's disease; it may occur in any patient with widespread brain disease. Discussion of treatment options with the family and the application of standard procedures outlined by Fitzgerald and Devakumar are as necessary in Parkinson's disease as they are in other conditions. The restrictions placed on the use of clozapine have made it difficult to employ this drug in patients with Parkinson's disease, despite evidence that it can be effective in controlling confusion and hallucinations without necessarily worsening parkinsonism. Risperidone (a potent serotonin 5HT<sub>2</sub> antagonist which also possesses dopamine D<sub>2</sub> antagonism) may prove to be a useful alternative, but further experience of its use in this situation is required. Ondansetron (a potent serotonin 5HT<sub>3</sub> receptor antagonist) is another drug that also may control neuropsychiatric symptoms of Parkinson's disease, but it is very expensive. There is a major need for safe, cheap, antipsychotic agents devoid of extrapyramidal side effects for use not only in schizophrenia but also in Parkinson's disease. Electroconvulsive therapy not only relieves severe refractory depression in Parkinson's disease, but also can improve the motor disabilities of that illness temporarily. It has been used in patients with advanced on/off fluctuations but unfortunately has had no useful sustained beneficial effect in that situation.