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Vasodilators in senile dementia

Before considering treatment for senile dementia the doctor must first ensure that the patient is not suffering from a reversible confusional state caused by infection, drug treatment, depression, or metabolic disturbance. He should then consider the possibility of an underlying treatable disease: 10-20% of younger people with dementia have a reversible cause for this.[1 2] A similar proportion might be expected in patients over the age of 75 years, but we have no evidence that accurate diagnosis and treatment alter the clinical outcome in older people, and hence few psychogeriatricians routinely submit their very old patients to detailed investigation.

Most demented old people have Alzheimer's type of senile dementia, which is characterised by a progressive downhill course, the patient usually having no insight into her mental deterioration. A smaller number have dementia associated with cerebrovascular disease. Vascular (or multi-infarct) dementia produces a stepwise decline, often with periods of insight. The patient, who may have a history of hypertension and stroke, usually has focal neurological signs and often shows emotional lability.[3] It is for this second group of patients that drug manufacturers recommend cerebral vasodilators. These are widely prescribed and are among the most profitable drugs in the world market.[4] How useful are they?

It was once thought that senile dementia was the result of impaired cerebral perfusion, which was caused by the narrowing of cerebral arterioles.[5] Drugs which dilated these vessels were expected to improve cerebral blood flow with consequent clinical improvement. This logic is faulty. In Alzheimer's dementia the reduced cerebral blood flow is the consequence rather than the cause of the disease[5]; an increased flow is unlikely to modify primary neuronal degeneration. In multi-infarct dementia the cerebral vessels are usually sclerosed and vasodilators are unlikely to have any effect on them. These drugs may, however, act on peripheral vessels and "steal" blood from the brain, producing a reduction rather than the expected increase in cerebral perfusion.

Not surprisingly, therefore, cerebral vasodilators have proved disappointing in clinical practice. None of the few studies on isoxsuprine has shown it to be of any practical value. This beta-adrenergic stimulant may decrease cerebral blood flow and its side effects include hypotension, flushing, and trembling. Cyclandelate has a direct action on smooth muscle, but its value in vascular dementia (or in any other vascular disease) has not been convincingly shown,[7] while its side effects include flushing, nausea, and rashes. This drug does not reduce cerebral perfusion, which suggests that it may have an action additional to simple vasodilatation.

A second group of cerebral vasodilators have an effect on cerebral metabolism in addition to their vascular action. The precise mode of action of these "cerebral activators" is uncertain, but the theory is that by improving the utilisation of oxygen and glucose by the brain they will be of practical value in cerebrovascular insufficiency. Dihydroergotoxine mesylate is a preparation of three hydrogenated alkaloids of ergot. It acts by alpha-blockade, and studies in animals show that it increases the activity of enzymes of intermediary metabolism in the ganglion. cells. A critical review of the clinical trials of this drug showed that only minimal improvement had occurred in a wide variety of indices of mental function, which differed from study to study,[8] while its side effects include sinus bradycardia[9] and hypotension. Prolonged administration of this ergot compound may lead to vascular insufficiency and gangrene of the fingers and toes, particularly in patients with pre-existing vascular disease.[7] Naftidrofuryl has several effects on cerebral metabolism, including an increase in the cerebral concentration of adenosine triphosphate and a reduction in that of lactic acid.[10] Several well-conducted studies have suggested that this drug improves memory and behaviour, but we need further studies to establish whether it improves activities of daily living.[6] Pentifylline is structurally related to caffeine and its conjugated with nicotinic acid. It may increase cerebral glucose uptake, but again we need more trials to assess its practical value.

A third group of compounds advocated for vascular dementia are the drugs that modify neuronal metabolism but have no vasodilator effect. Meclofenoxate[11] reduces the needs of the brain for oxygen, and pyritinol hydrochloride (not available in the United Kingdom) increases cerebral blood supply.[12] Yet again, we need more studies to evaluate these drugs.

The difficulties in mounting clinical trials in dementia are legion, and it will be some time before we reach any firm conclusions about the effectiveness of cerebral vasodilators. On present evidence, it appears that simple vasodilators have no place in the treatment of vascular dementia. They have few demonstrable therapeutic effects and they may be harmful. "Cerebral activators" (with or without a vasodilator effect) are of theoretical interest. They have been reported to show

variable improvement in mental function, but we do not know which patients (if any) will benefit from them or for how long treatment should continue. Whether a doctor prescribes them or not is therefore largely a matter of temperament.

It cannot be overemphasised that drug treatment is only a minor part of the management of dementia. Indeed, by making the doctor feel that he is doing something, the administration of these drugs may actually deflect him from the really important tasks: providing the patient and family with sympathy, practical advice, and social support.[13-15]

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Gastric and duodenal ulceration after burns

Although ulceration of the stomach and duodenum after burns was first described by Swan in 1823 (and described by Curling in his classic account in 1842), we still know little about how this occurs. As early as five hours after burning the lining of the stomach and duodenum may show congestion, oedema, mucosal haemorrhages, and multiple superficial erosions[1]—while from three days onwards true gastric and duodenal ulceration may be present. Serial gastroduodenoscopy has shown that ulceration is a more advanced stage of a disease which began soon after burning.

The condition is common. In 1965 in Birmingham a fifth of burned patients examined at necropsy were found to have ulcers in the stomach or duodenum, or both,[2] while in 1970 at the United States Army Burns Centre just over a tenth of all treated burned patients had clinical or necropsy evidence of this.[3] In a subsequent prospective study of 54 burned patients examined by early and serial fibreoptic gastroduodenoscopy Czaja *et al*[4] found acute gastric erosions in four-fifths of patients and acute gastric ulceration in a quarter. Acute duodenitis was present in three-fifths of patients, and acute duodenal ulceration in a fifth. The frequency of ulceration increases with the total area burned: the peak incidence is 40% in those patients who have 70% of the body surface burned.[3]

An unexplained difference exists between the commonness of haemorrhage and perforation from these ulcers in the United States and their infrequency in Britain. Thus in Pruitt's series ulceration was clinically evident (as shown by haemorrhage) in two-thirds of the patients and showed no clinical manifestations at all in only a quarter of the cases.[3] In Sevitt's series of 64 cases of ulceration noted at necropsy, on the other hand, only three were clinically evident.[2] This contrast persists.

Surgery is indicated for uncontrollable haemorrhage or perforation, the usual operations being subtotal gastrectomy or vagotomy and antrectomy. At operation the surgeon has to remember that gastric and duodenal ulcers coexist in 15% of cases.[3]

Gastric acid secretion is not increased in states of stress but it must be present for stress ulcers to form. In rats subjected to cold-induced stress pretreatment with cimetidine reduced the number of gastric mucosal erosions:[5] however, intragastric administration of hydrochloric acid after pretreatment with cimetidine abolished this favourable effect. Hence the benefit of cimetidine could be due to a reduction of gastric acid production. Certainly clinical regimens that reduce gastric acid are considered essential in the United States for preventing haemorrhage, which typically presents about 15 days after the patient is burnt. Solem[6] treated 109 patients with extensive but non-lethal burns with one of three regimens (intensive antacid therapy, an elemental diet, or both) all designed to reduce gastric acid, and all of these protected the patients from clinically evident ulceration—that is, from haemorrhage and perforation. Whereas the results of studies before the use of antacid therapy suggested that 14-26 of these patients would have been expected to develop clinically evident ulceration, in fact only three patients did so. Nevertheless, the regimens did not prevent clinically occult ulceration, and we need further studies to indicate their role in routine clinical practice.

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Acquired pulmonary stenosis

Pulmonary stenosis is usually congenital but may be acquired, though sufficiently infrequently to be described in case reports.[1] The stenosis may be extrinsic, from compression of the low-pressure right ventricular outflow tract and pulmonary artery, or intrinsic, from obstructing lesions of the pulmonary valve and infundibulum of the right ventricle. The most common extrinsic causes are anterior mediastinal tumours, often lymphomas, although others include secondary carcinoma and thymoma.[2-4] Any mass in the anterior mediastinum may compress the right ventricular outflow tract, and minor obstruction is not uncommon with aortic aneurysms, particularly those of the right sinus of Valsalva.[2] Pericardial disease may be localised, and constrictive pericarditis may present as pulmonary stenosis.[5]

The best-recognised cause of acquired stenosis of the pulmonary valve is the malignant carcinoid syndrome.[6] The valve is rarely affected by rheumatic fever, although this complication may be more common in those living at high altitudes.[7] Among the other intrinsic causes of pulmonary stenosis are cardiac tumours—for example, myxoma[8]—and hypertrophic cardiomyopathy. The latter affects the ventricular septum and usually presents with the symptoms and signs of obstruction of the left ventricular outflow tract. The right