

## TODAY'S DRUGS

*With the help of expert contributors we publish below notes on a selection of drugs in current use.*

### Cyclandelate

This drug is marketed by Brocades (Great Britain) Ltd. under the name Cyclospasmol.

The place of vasodilator drugs in the treatment of patients with vascular insufficiency is controversial. There is a need for effective drugs to relieve the symptoms of claudication in patients with obstructive disease of the leg arteries. Similarly, patients with cerebrovascular disease present an intractable therapeutic problem, particularly those with recurrent episodes of circulatory insufficiency. Evidence of the efficacy of drugs used hitherto is unsatisfactory. Cyclandelate is a vasodilator drug discovered in 1952 whose use is recommended by its manufacturers in both of these conditions.

### Pharmacology

Cyclandelate (3,5,5-trimethylcyclohexanol) is one of a series of substituted derivatives of mandelic acid that were examined by Funcke<sup>1</sup> in 1952. Funcke's thesis is not readily accessible although his findings are summarized in a paper by Van Wijk.<sup>2</sup>

Cyclandelate is a vasodilator acting directly on vascular smooth muscle. It is effective when given by mouth, and in animals it reduces the spasm of vascular smooth muscle induced by injection of barium chloride and is more potent than papaverine. It does not cause hypotension or tachycardia, which suggests a relatively weak acute vasodilator effect.

The acute toxicity of the compound in animals is low, the L.D.<sub>50</sub> being of the order of 5 to 10 g./k. Chronic toxicity studies also suggest that there is a wide margin of safety between doses used in therapy and those likely to cause deleterious effects.

There is relatively little quantitative information concerning the pharmacological effects of cyclandelate in man. O'Brien and Veall<sup>3</sup> studied the effects of large single doses of the drug on cerebral cortex perfusion rate in a group of nine patients with cerebrovascular disease. There was a significant increase in cortical blood flow measured by the xenon clearance method, averaging 6.5 ml. per 100 g. per minute in these studies, which were carried out four to six hours after an oral dose of 1 g. of cyclandelate. There was little change in blood pressure following this dose.

### Therapeutic Efficiency

Several large series of patients treated with cyclandelate have been reported in the literature, but none has included a comparison with placebo or another vasodilator drug.

Van der Drift<sup>4</sup> reported results in 200 patients with ischaemic cerebral disease given 200 to 600 mg. cyclandelate daily. In 72 of 120 patients with transient cerebrovascular attacks he found a good to marked improvement. No control group was used, but 7 of 10 patients whose treatment was stopped had a recurrence of their attacks. Several authors have reported series of patients with peripheral arteriosclerotic vascular disease or Raynaud's phenomenon who have been treated with the drug. Gillhespy<sup>5</sup> found that nearly half his patients with Raynaud's phenomenon or claudication were rendered symptom-free by treatment with cyclandelate in a dose of 100 mg. three times

daily. Van Wijk<sup>2</sup> treated 50 patients with 300 to 600 mg. daily and found that slightly over half were improved. He noted mild nausea, heartburn, constipation, and palpitation in some of them. Ross<sup>6</sup> measured the claudication time in a group of 10 patients before and during treatment with 100 to 300 mg. orally four times a day. He found an improvement which began after about six weeks of treatment and increased for six to ten weeks.

### General Considerations

Apart from the proved efficacy of nitrites in relieving anginal pain, completely convincing evidence for the usefulness of vasodilator drugs in patients with vascular insufficiency is scanty. If a vessel feeding an ischaemic area is completely obstructed or severely narrowed it is unlikely that any drug can have a direct effect upon it. If it had a useful action it would have to be upon collaterals. Furthermore, this effect on collaterals should be selective, as vasodilatation in normal areas might shunt flow away from the ischaemic area. The usefulness of an unselective drug will be limited by the hypotension and tachycardia which results from a general vasodilatation throughout the systemic circulation.

If blood flow to an area is reduced by reversible local factors such as smooth muscle activity (vasospasm) or embolization by platelet aggregates the situation is somewhat different. It is conceivable that vasospasm might be relieved by a drug, with benefit to the tissues downstream, but it appears unlikely that such an effect would develop over a period of weeks. Narrowing of the coronary vessels can sometimes be acutely reversed by nitrites,<sup>7</sup> but there is no evidence that cyclandelate has a similar action.

Cyclandelate causes a moderate increase in cerebral blood flow when given in a single large dose, but this is no guarantee that it will be of benefit to patients suffering from regions of impaired cerebral perfusion. The uncontrolled therapeutic trials that have been published do not provide sufficient proof that the drug has a beneficial effect. More evidence on this point is necessary.

As many cerebrovascular attacks are transient and intermittent claudication often improves with time it may be useful to determine whether a patient's improvement on cyclandelate can be maintained after stopping the drug.

It is important to remember that treatment with a vasodilator affords, at best, only symptomatic relief in a patient with vascular disease. A search for other treatable factors such as hypertension, diabetes, obesity, excessive smoking, or surgically correctable stenosis of large arteries should always be made.

### Dosage and Cost

The usual starting dose is 100 mg. three times daily. This can be increased up to 400 mg. three times a day.

Cyclandelate is available as Cyclospasmol in 200-mg. tablets. The basic N.H.S. cost of 50 tablets is 21s. 2d.

### REFERENCES

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