USE OF IPRONIAZID IN ISCHAEMIC ANGINA PECTORIS

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Iproniazid ("marsilid"; 1-*iso*nicotinyl-2-*iso*propyl-hydrazine phosphate), a derivative of isoniazid, was found by Cesarman (1957) to relieve angina pectoris in a patient who was given the drug for its effect on mood. Cesarman followed up this observation in 40 patients with angina pectoris and showed that iproniazid reduced the frequency and severity of their attacks.

We have carried out a preliminary trial with iproniazid in 40 patients with angina to evaluate its effectiveness, to investigate its mode of action, and to assess its place in treatment.

Method

All 40 patients had frequent angina pectoris. Most had pain on slight effort such as walking a few steps, and some had rest pain also. In 24 patients the situation was deteriorating and in 16 it was static. In all but five the electrocardiogram showed changes of previous cardiac infarction or present coronary insufficiency. All patients received other routine treatment such as bed rest, anticoagulants, and trinitrin, if those seemed to be indicated. Long-acting nitrites were not given. Iproniazid was prescribed in doses of 50 mg. two or three times daily.

Results

Patients began to improve five days to one month after starting treatment, the average period being about two weeks. After one month of treatment 17 patients had pain only occasionally, and much greater effort was required to provoke it. A further 14 patients were improved but still had angina on moderate effort. Of the remaining nine patients, one has died, four were unchanged, and four had stopped the drug after a week or two because of side-effects. Nineteen patients have been followed for three months or more and the improvement has been maintained in all but two.

After one month the electrocardiogram was improved in 9 patients, unchanged in 19, and worse in 5. Of the patients followed for three months or more the electrocardiogram improved in the majority, but was unchanged in four and worse in two. Two patients with the changes of coronary insufficiency, which were reversible with trinitrin, became free of pain despite the persistence of these changes.

Side-effects

Side-effects occurred in most patients after one to four weeks of treatment. The commonest was giddiness (lightheadedness), which was present in 15 patients. Usually it was mild and temporary, but in five patients it was severe, and the drug had to be stopped. Two of these patients fainted. Syncope was associated with a fall in blood pressure and was presumably vasomotor rather than cerebral in nature. In one patient who complained of dizziness the blood pressure fell from 200/110 to 110/70 while on iproniazid. In the whole series the average fall in systolic pressure was 15 mm. Hg. Impotence was common amongst the men, but was not resented by elderly patients.

A rapid increase in weight of the order of 14 lb. (6.4 kg.) in a month occurred in four patients, and was associated with a voracious appetite in two of them, but not in the other two. In the majority of patients, however, there was little or no gain in weight.

Greater confidence, a lightening of mood, or frank euphoria was the rule in patients treated with iproniazid, and proved a therapeutic ally, tending to prevent patients taking a pessimistic view of other side-effects.

Three patients complained of twitching of the limbs, two of weakness in the legs, three of constipation, and two of frequency of micturition. Ankle oedema with a rise in jugular venous pressure appeared in two patients, but cleared rapidly when the drug was withdrawn and did not return on restarting it. Two patients complained of breathlessness and showed pulmonary oedema and Kerley lines on *x*-ray examination. There was no triple rhythm or change in heart size. The lung changes cleared in one patient within 10 days of stopping iproniazid, without other treatment. The other patient received mercurial diuretics in addition, but remained well when these were withheld.

In two patients in whom iproniazid was stopped after a short period, the pain returned in about 10 days. Isoniazid was substituted in one patient and was found to be ineffective. Two patients, one with severe giddiness and one with peripheral oedema, insisted on restarting iproniazid because while on the drug they were free from pain for the first time in several months.

In an editorial (1958) liver damage has been reported in patients receiving iproniazid. Ten of our patients were receiving anticoagulants, which interfere with the hepatic synthesis of prothrombin, when treatment with iproniazid was started. The drug did not produce increased sensitivity to the anticoagulants. No evidence of hepatic disorder was detected in any of our cases, but liver-function tests were not carried out routinely.

Discussion

In this preliminary study we decided to dispense with a control series because of the powerful effect of iproniazid on anginal pain reported by Cesarman (1957) and Cossio (1957, 1958). We consider that this decision has been amply justified and confirm that the drug relieves angina pectoris. It is much more effective in this respect than the long-acting nitrites. Its action cannot be accounted for by the euphoria it sometimes produces. It may relieve pain although the electrocardiogram deteriorates. In this small series of patients with crippling angina pectoris relieved by iproniazid, the serial electrocardiographic findings and mortality rate were such as might be expected from routine treatment alone; there was no evidence that iproniazid influenced the natural history of the disease. On the basis of similar observations Cossio suggests that the drug acts by a selective analgesic action on muscle pain of ischaemic origin. It has since been shown to relieve pain in certain cases of carcinomatosis and rheumatoid arthritis, and it may be that the drug acts by blocking pain in the central nervous system. Its most powerful known pharmacological action is the blocking of monoamine oxidase activity, and it is thought that some or all of the observed clinical effects may be due to this.

Undue exertion may precipitate cardiac infarction in patients with coronary artery disease (Yater *et al.*, 1948). Iproniazid, by blocking warning pain, may increase the risk of infarction, and anticoagulant protection is theoretically desirable for patients on iproniazid.

Severe and recurrent anginal attacks frighten, depress, and exhaust the patient and presumably lower the threshold for pain. Iproniazid can help dramatically by its pain-blocking and euphoriant actions, and there is a real place for it in the treatment of such patients. It should be continued for two or three months or until the electrocardiographic changes of coronary insufficiency, if present, have resolved. The drug can then be withdrawn in order to assess the

situation on the basis of the number of anginal attacks and the effort required to produce them. It should always be stopped before the patient returns to work.

Because of the danger of masking myocardial ischaemia, the numerous side-effects, and the risk of serious liver damage, iproniazid is not indicated for the patient with mild angina.

Although the drug could theoretically give rise to "silent infarction," this did not happen in any of our patients. Two of them had infarcts while receiving iproniazid. Both were at rest at the time and had typical pain.

The side-effects of iproniazid are described by Robitzek and Selikoff (1952) as, firstly, those referable to autonomic stimulation, including dryness of the mouth, constipation, delayed micturition, and difficulties in visual accommodation; secondly, those referable to central nervous system stimulation, including vertigo, muscle-twitching, hyperreflexia, excitement, euphoria, somnolence; and, thirdly, those referable to antagonism to vitamin B, including peripheral neuropathy. Unfortunately these and other side-effects limit the usefulness of the drug.

Summary

Iproniazid has been given to 40 patients with severe angina pectoris from occlusive coronary atherosclerosis, and was highly effective in reducing the frequency and severity of anginal attacks. It appears to act by blocking pain and not by improving the coronary circulation. Side-effects are common; many of our patients complained of giddiness and two developed pulmonary oedema, presumably from fluid retention. The blocking of angina may encourage the patient to be more active and may precipitate infarction. Because of this and the side-effects, the drug is not indicated for patients with mild angina pectoris. In the patient with severe and intractable angina it is of great value, especially if anticoagulant therapy can be given in addition. The patient can often be helped over a prolonged ischaemic episode, the drug being withdrawn when the condition improves.

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"We have learnt a great deal during the last three years from three reactor accidents which have led to partial melt-out of the reactor fuel elements. Although two of the reactors were put out of commission for a year and one was written off, no one was hurt by these accidents or received an overdose of radiation. The results of the accidents agree in a remarkable way with laboratory experimental work in showing that only a very small fraction of some of the bone-seeking isotopes escaped from the melted fuel. The disturbances due to these accidents were accordingly less than envisaged previously. Later generations of reactors than these early models are much better protected by containment and instrumentation, and some papers have shown considerable progress in advanced designs of containment which are thought to be proof against the maximum credible accident. This gives us considerable confidence in safe operations in the future, and we may, in due course, expect the location of plants in more populated areas. There has also been a growth of national reactor safety and inspection organizations, analogous to those in being for the aircraft industry. They inspect designs and prescribe codes of operation to help to maintain safety."—From a lecture by Sir JOHN COCKCROFT, F.R.S., to the Danish Society of Civil Engineers on October 6.

JAUNDICE ASSOCIATED WITH ADMINISTRATION OF IPRONIAZID

REPORT OF TWO CASES

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Iproniazid ("marsilid"; or 1-*iso*nicotinyl-2-*iso*propylhydrazine phosphate) is a variant of isoniazid, which was first used for its antituberculous properties in 1952. Then described as a drug which made patients "dance and sing in the ward" and as a "fountain of energy," it was discarded by chest physicians as too apt to produce side-effects, including psychotic episodes; it has since been hailed by psychiatrists as a powerful "energizer," and been found useful in the treatment not only of depressive states but also in angina pectoris and collagen diseases, gastro-intestinal conditions, etc. Zeller *et al.* (1952) found that iproniazid was a powerful inhibitor of amine oxidase. Udenfriend *et al.* (1957) were able to demonstrate a rapid and large rise in brain serotonin in animals given the drug. The effect of the drug on mood in humans has been attributed to this increase in serotonin.

In a symposium (1958) in New York in 1957 many preliminary studies were presented, but concluding speakers stressed the need for carefully controlled trials before definite claims for the value of the drug in psychiatric and other conditions could be made. During the course of such a trial in this hospital, two cases of jaundice have occurred. The possibility of this drug being hepatotoxic has recently been raised. In view of the increasing use of iproniazid in psychiatric practice, these cases seem worthy of immediate report.

Case 1

The patient, a 53-year-old working-class widow, had been subject to spells of agitation and depression, with increasing suspiciousness and misinterpretation for three years. She was previously hardworking and loyal, and had struggled to bring up five children, one of whom was diabetic from infancy. She had had no serious illness previously, and had never been jaundiced. She had not received injections and there was no contact with cases of infective hepatitis.

She was admitted to hospital on October 11, 1957, and made a good initial response to hospitalization. Iproniazid was first given at 150 mg. daily on January 11, 1958, and reduced to 100 mg. daily on February 11. During the first week of March she began to feel vaguely unwell, suffered from giddiness and palpitations, and later complained of superficial pains in the limbs and shivering attacks. All but the latter symptoms have been described as side-effects and are often encountered in iproniazid therapy. Our patient minimized these for fear that she might be taken off the drug, which was helping her considerably. On March 24, however, she developed mild anorexia with constipation and took to her bed. Iproniazid was discontinued. Two days later, though subjectively much improved, she was jaundiced and had a pale stool and biliuria.

On examination the liver edge, slightly tender, could be palpated two fingerbreadths below the costal margin, but liver dullness was not greatly increased. She was, and remained, apyrexial. (For details of investigations, see Table.) With a low-fat diet, rest, and vitamins her strength and