THE EFFECT OF NIKETHAMIDE BY MOUTH IN MAN

BY

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Nikethamide was introduced as a therapeutic agent about twenty-seven years ago under the trade name of "coramine." It is also known as "anacardone," "corediol," "corvotone," "nicamide," and "niketharol." This paper deals with the effects of the drug administered by mouth in man. The study has been prompted by the apparent difference of opinion which exists about its therapeutic value when given by this route.

Faust (1925) states that the drug is active when given by mouth, but does not make it clear if this refers to the human subject; Kohlhoff (1928) found that the convulsant dose in the rabbit by mouth was five times as great as the convulsant dose by intravenous injection. Dodds (1936) states that it exhibits a very powerful action in small doses by mouth in experimental animals. There are a number of references to the value of oral nikethamide in the treatment of cardiac dyspnoea, coronary artery disease, and peripheral circulatory failure, but the published details are inconclusive (Lankford, 1930; Daly, 1933; Winslow, 1936; Timmons, 1937; Lerner, 1937; Cowan, 1937, 1938; Stroud and Twaddle, 1940; Gayid, 1952; Morwood, 1952). The *British Pharmacopoeia* assigns it an oral dose of 0.25–1 g. or 1–4 ml. (as it is always used in a 25% solution), which is the same as the dose by parenteral injection, and it is employed especially in general practice in this dose, usually three times daily. The current editions of the standard textbooks on pharmacology and therapeutics, on the other hand, are not enthusiastic about its oral use, statements such as "of doubtful efficacy" or "not very powerful" being the rule. Modern textbooks on cardiology do not mention its use by mouth (Wood, 1950; White, 1951). It therefore seemed worth while to find out whether the actions of the drug, as seen after parenteral injection, could be reproduced in conscious subjects by oral administration.

Clinical Trial

Briefly the effects of 4 ml. given *intravenously* in the conscious subject are as follows. Pain is felt along the line of the vein, and within 10–15 seconds obvious hyperpnoea occurs, with usually but not always an increase in the rate of breathing. At the same time the patient experiences a feeling variously described as "hot and cold," "funny feelings," "pins and needles," throughout the body and especially in the face, fingers, and toes. The blood pressure and pulse rate rise to a variable degree, and sweating about the hands and face occurs; the whole effect is remarkable for its short duration, being completely over in a few minutes. In apprehensive subjects greater changes in the pulse rate, blood pressure, and respiratory rate are seen than in those who are less nervous, but the hyperpnoea and subjective paraesthesiae are invariable. It was thought that these effects might be reproduced by oral administration. A dose of 5 ml. five times daily was given to eight different subjects on ten different occasions for periods varying from 3 to 26 days, and records of the pulse rate, respiration, and blood pressure were taken frequently. In addition urinary output and electrocardiograms were recorded in some cases. All

these patients had been observed in hospital for a prolonged period. All suffered from chronic heart failure with dyspnoea, and oedema was present in four cases. In four subjects nausea occurred and some doses were vomited, but otherwise the results were negative.

An attempt was then made to obtain some obvious effect by increasing the dose to 10 ml. five times daily. This dose was given to four different subjects, but in all of them it had to be abandoned after three to four days because of nausea and vomiting. Significant changes in the pulse and blood pressure did not occur and changes in breathing were not seen apart from those associated with nausea and the act of vomiting.

Single doses of 16 ml. were given to six subjects: four had chronic heart failure, one suffered from bronchial asthma, and one was a healthy subject. Nausea was experienced by all six patients and vomiting occurred in two, but again no effects such as are seen after intravenous injection were noted.

Finally, doses of 30 ml. were given to three subjects, all suffering from chronic heart failure. In one the dose was promptly vomited. In the other two it was retained with encouragement, though considerable nausea was produced, but no significant changes were seen in the depth and rate of breathing nor in the pulse and blood pressure.

Comment

In all, nikethamide has been given in these large doses to 20 different subjects without any indication of effect apart from nausea and vomiting. It would seem that the characteristic action of the drug is hard to obtain by oral administration, and it is very doubtful indeed if in the doses in which it is commonly given (1–2 ml. three times daily) it can have any pharmacological action of therapeutic value. Indeed, these small doses barely produce any effect even when given intravenously.

It is realized that the simple methods of bedside observation which have been employed may not have been sensitive enough to record minimal changes, but the therapeutic value of the drug is best ascertained by these clinical techniques. An attempt is now being made to evaluate the drug on the basis of blood levels of free nikethamide attainable by the various routes of administration. Probably the main value of this biochemical development will be to throw further light on the metabolism of nikethamide, which in turn may account for the failure of the drug to produce its characteristic action when given by mouth to the human subject.

Summary

Nikethamide was administered orally in doses of 5 ml. and 10 ml. five times daily, and in single doses of 16 ml. and 30 ml. It produced no effects on the cardiovascular or respiratory system. When symptoms and signs of cardiac failure were present they were not affected by the treatment.

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