Dicoumarol Therapy

Dosage.—It must be clearly understood that there is no standard dose of dicoumarol, and that the reactions vary greatly with different patients. For this reason it is essential that prothrombin estimations should be carried out at regular intervals. Many workers recommend daily estimations. I have found that estimations on alternate days are sufficient, except during the initial stages of treatment—that is, for the first four or five days—and in those cases with widely fluctuating clotting-times that sometimes occur. One factor of great importance with regard to dicoumarol dosage is the age and general condition of the patient. The older and more frail the patient is the more susceptible is he to dicoumarol—so much so that I give a reduced dosage to all those over 65 years. Of six patients who had haemorrhages all but one were over 65. It is important to remember that some patients are much older than their years, and vice versa; and this factor should be borne in mind when using dicoumarol. Some patients are very susceptible to dicoumarol, and haemorrhages can occur with a very small dose: one patient, aged 69, had serious bleeding with a total dose of only 550 mg. of dicoumarol.

Scheme of Dosage.—For younger patients: First day, 300 mg.; second day, 200 mg.; third day, 200 mg.; and then a daily dose of 50 mg., to be varied according to the prothrombin clotting-time. Many young robust people are relatively insensitive to dicoumarol and will need larger doses—for example, 100 mg. daily instead of 50 mg. to keep the prothrombin at a therapeutic level. For older patients (65 years and over): First day, 200 mg.; second day, 200 mg.; third day, 100 mg.; and then 50 mg. daily, to be varied according to prothrombin clotting-time. In the initial stages it is better to give dicoumarol in small divided doses than in a single large dose.

Most authorities usually give an initial dose of 300 mg. of dicoumarol followed by 200 mg.; they then give it according to the prothrombin content as ascertained by daily estimations. I find, however, that this method tends to produce a fluctuating curve. I therefore prefer to give a small daily dose of dicoumarol after the initial heavier dosage—omitting the drug, of course, if the prothrombin falls to a dangerously low level.

In practice I have found the daily microscopical examination of urine for red cells very useful. In many cases their presence foreshadows an impending gross haemorrhage, and as soon as any quantity appear dicoumarol must be stopped.

Conclusions and Summary

Estimation of prothrombin has assumed a greater clinical significance since the use of dicoumarol. Practical difficulties in carrying out the test are mainly due to the inability to standardize and prepare thromboplastin. Quick's method is a simple one, and most convenient for clinical use. The commonly used method of diluting whole plasma with saline in order to bring out an early fall in the prothrombin level is not advocated.

A simple method of preparing a stable and active thromboplastin preparation is essential. The most frequently used preparations are Quick's original acetone-dried brain extract and Russell-viper venom. The latter often gives false low clotting-times, with the consequent danger of overdosage with dicoumarol and subsequent haemorrhage. Preparation of acetone-dried brain extract usually requires skilled technical ability.

A description is given of an alternative and simple thromboplastin preparation made by emulsifying human brain with normal saline to which has been added 0.5% phenol as a preservative.

A thromboplastin preparation which will give a prothrombin clotting-time with normal plasma of 13 to 16 seconds is advised. This preparation usually corresponds with the 150-mg. tube as used in cerebrospinal fluid protein estimations.

For effective dicoumarol therapy a prothrombin clotting-time of 30 to 50 seconds is advised. It is not essential to record the prothrombin level as a definite percentage. The absolute clotting-time is considered of much greater clinical importance, and, using an active thromboplastin preparation which gives a clotting-time of 13 to 16 seconds with normal plasma, it is sufficient to maintain a clotting-time of 30 to 50 seconds.

Dicoumarol varies in its activity in different people, some being very susceptible to small doses. This is especially so with the elderly and the frail, who should be given a reduced dose. Conversely, the young and robust will stand much larger doses. After the initial heavier medication to lower the prothrombin to the required therapeutic level, a small daily dose is advocated. In the majority of cases it will suffice to estimate the prothrombin level on alternate days after the first four to five days of treatment. A scheme of dosage which has been found in practice to give adequate treatment is outlined. Daily microscopical examination of the urine for the presence of red cells is of value as an indication of the likelihood of more serious haemorrhage occurring.

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IODINE AND GASTRIC FUNCTION

BY

G. PAPAYANNOPOULOS, M.D.

Lecturer in Clinical Medicine, University of Athens School of Medicine

A great number of papers have been written on the influence of iodine and its derivatives on the function of the stomach. The most important question is whether the gastric mucosa has the ability to secrete iodine introduced intravenously or to absorb it. Rose (1930) first presented evidence that the gastric mucosa has this ability. His evidence was confirmed by experiments in animals and men by Pentzold and Faber (1897) and Nencki and Schoumow-Simanowsky (1894). The last-named authors came to the conclusion that it is possible for the gastric mucosa to replace the hydrochloric acid in small part by hydroiodic acid. This conclusion corresponds with that of Lipschitz, who found that the ability of the gastric mucosa of the rabbit to secrete iodine is almost comparable to that of the kidneys. As pointed out by Heilmeyer and Sturm (1928), iodine begins to be secreted by the gastric mucosa while it is still in the peripheral circulation.

This ability of the gastric mucosa to secrete iodine led me to investigate the influence this secretion had on stomach

function and especially on its chemistry, and to see if it is possible to utilize this property as a gastric-function test. Such an attempt was made by Sahli and Strauss (quoted by Schulz, 1934), but without practical results. More valuable findings have been obtained by Henning (1930). He pointed out that the introduction of iodine through a small tube in a stomach the mucosa of which was impaired was followed by the appearance of that substance in the saliva. If the mucosa was intact iodine was absent from the saliva.

Present Investigations

For my investigations I chose 35 adult patients who suffered from various stomach diseases. The technique used was as follows: The patient was prepared as for a basal metabolic test. A duodenal tube was passed so that its tip reached the lowest part of the stomach. The patient was urged not to swallow saliva, and this caution was emphasized throughout the test. After the fasting secretions had been collected, aspiration was continued over fifteen 10-minute periods. The material obtained was placed in graduated tubes. The volume of secretion and the amount of free acid and total acid in the contents of each tube were then estimated. The whole procedure was repeated two days later after the intravenous injection of 5-10 ml. of a 10% solution of sodium iodide (0.42-0.84 mg. of iodine). If there was bile-staining the results were discarded and the test repeated another day.

The cases were divided into three groups. Group I consisted of patients with acute and chronic duodenal ulcer. They came to the clinic complaining of periods of distress, night pain, vomiting, and constipation. When admitted they had had no previous medical care. Measurement of their fasting secretion showed a large volume of juice, the total acidity of which was 70 to 90 degrees. After the intravenous injection of 0.42-0.84 mg. of iodine the total acidity was higher than before, often reaching 100-130 degrees (Fig. 1). It was observed that the free acid and total acid rose according to the intensity of the inflammation of

FIG. 1.—Total acidity after intravenous injection of 0.42-0.84 mg. of iodine in a patient of Group I.

the gastric mucosa. In one such patient the total acidity reached 150 degrees. According to Portis and Bloomfield (1944) only after the histamine test is it possible to obtain such high degrees of acidity.

Group II mainly consisted of patients with stomach ulcer. A few also had duodenal ulcer. The acidity of the gastric

FIG. 2.—Showing the reaction of the gastric mucosa to the injection of 0.42-0.84 mg. of iodine in a patient of Group II.

juice of all patients was normal or nearly normal. The total acidity was never higher than 70 degrees. Doses of 0.42-0.84 mg. of iodine were injected intravenously before or during aspiration of the juice. Fig. 2 shows that the reaction of the gastric mucosa to the injection of iodine was not as strong as in patients of Group I. Nevertheless the amount of free and total acid was 20 to 40 degrees higher than before the iodine test. From these figures it can be concluded that the ability of

the gastric mucosa to secrete, after the iodine test, a highly acid juice did not last more than two hours. The degree of acidity began to drop after the first hour.

Group III was composed of patients with chronic alcoholic gastritis, functional achlorhydria, gastritis due to Addison's anaemia, etc. The intravenous injection of iodine in the form of sodium iodide remained without any effect. Only those with alcoholic gastritis showed a slight increase in the total acidity (Fig. 3). It is important to note that the results obtained in Group III were very similar to those obtained after the test with histamine, which is the most powerful known stimulus to gastric secretion.

FIG. 3.—Effect of the intravenous injection of sodium iodide in a patient of Group III.

Comment

In analysing the effects of iodine on the gastric mucosa one is confronted with the appraisal of many factors that can influence gastric secretion. One of the most important is the effect of emotion. According to Wittkower (1935) fear, disgust, sadness, anger, and apprehension during the course of an aspiration depress the secretion in some subjects, while in others they increase it. There are still many gaps in our knowledge of the mechanism of gastric secretion. Therefore it is very difficult to state what causes the increase of gastric acidity after the intravenous injection of iodine. It has been suggested that this increase is due to the hydroiodic acid which is formed in the stomach after introduction of the iodine. This opinion is based on the results of investigations of Nencki and Schoumow-Simanowsky (1894) on dogs which were given sodium iodide. But the amount of hydroiodic acid found in the stomach of the dogs was very small. Furthermore, the investigations of Batke (1917) showed that hydroiodic acid is not a normal substance of the body, as are hydrochloric acid and hydrobromic acid; therefore it is not possible for the gastric mucosa to replace the hydrochloric acid by hydroiodic acid.

I believe that the post-iodine hyperacidity seen in the patients of the first two groups was the result of a continuous excessive stimulation of the parietal cells by the iodine which these cells probably secreted. The fact that in patients with alcoholic gastritis and gastritis due to Addison's anaemia no increase of the total acidity was noted after the iodine test further supports my opinion. One must also keep in mind that in these cases the histamine secretion was variable and sometimes did not produce free acid. In the first two groups the results after the histamine test were very similar to those obtained after iodine. The lack of any reaction to iodine or to histamine in the patients of the third group must be attributed to the destruction of the parietal cells. Without doubt histamine is a powerful stimulus of gastric secretion, but from my observations in the three groups of patients I find that in place of histamine we can use iodine. Furthermore, iodine is less harmful than histamine.

Summary

A clinical and laboratory study has been made of the influence of iodine on the function of the stomach.

Investigations showed that, after intravenous injection of 0.42-0.84 mg. of iodine in the form of 5-10 ml. of a 10% solution of sodium iodide in patients with duodenal and gastric

ulcer and acute gastritis, the amount of free and total acid was 20-40 degrees higher than before.

In patients with alcoholic gastritis the iodine test had no effect.

The results obtained after the injection of iodine were similar to those obtained after the histamine test.

Therefore it would be better to replace histamine by iodine in testing for gastric function.

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HYPERSOMNIA SYNDROMES

BY

M. N. PAI, M.B., M.R.C.P., D.P.M.

Psychiatrist, Belmont Hospital, Sutton

During recent years there has been a tendency to describe syndromes in which somnolence or hypersomnia has been associated with other symptoms. Some have reported cases of periodic somnolence and morbid hunger (Kleine, 1925; Lewis, 1926; Levin, 1929, 1936, 1938; Kaplinsky and Schulmann, 1935; Critchley and Hoffman, 1942; Ronald, 1946), and a few have described patients suffering from hypersomnia at menstrual periods (Kleine, 1925; Lhermitte and Kyriaco, 1929; Lhermitte, 1942; Lhermitte, Hécaen, and Bineau, 1943). Episodic states of sleep have also been reported by workers at the Frankfurt Clinic (Grosch, 1943). It has been claimed that all these syndromes exist as definite entities.

Clinical Material

In a survey of 2,169 in-patients treated by me in E.M.S. neurosis hospitals during the period 1940-8 there were cases of nearly every kind of psychiatric illness, including a wide variety of sleep disturbances (Pai, 1946b). The present paper is based on a study of 67 male patients who complained either of diurnal somnolence or of hypersomnia. Somnolence is here used to mean drowsiness during which a person is partially aware of what is happening around him. Hypersomnia is a condition in which daily more hours are spent in sleep than in wakefulness. Cases of narcolepsy have been excluded from this study. The ages of these patients ranged from 18 to 27, with an average of 22.6 years. The methods of obtaining social histories and independent factual evidence and of assessing personality have been discussed elsewhere (Pai, 1944, 1945, 1946a).

The Wassermann test was done as a routine, and special investigations such as the fractional test meal, x-ray examination, and electroencephalography were carried out in

appropriate cases. The staff had strict instructions not to give more than the authorized scale of rations, and individual requests from patients for extra food were ignored.

Clinical investigations consisted chiefly in testing the plantar reflex at intervals and in noting the presence or absence of vocal and motor activities (a) during the period of apparent sleep, (b) during apparent sleep induced by hypnosis, and (c) during narcosis produced by giving intravenously a 10% solution of a barbiturate such as "sodium amytal." The object of these procedures was partly to estimate the approximate duration of physiological sleep and the time spent in the transitional stages between full wakefulness and sleep, and partly to determine which physical signs gave the most reliable indications of sleep.

It was ascertained that the period of so-called sleep consisted of phases of physiological sleep interspersed with waves of partial sleep. Vocal and motor activities were either absent or infrequent during spells of sleep and were more frequent during the intervals of partial sleep. The average time spent in sleep was roughly about four and a half to five hours (Pai, 1949).

Psychiatric Findings

Personality studies and psychiatric investigations revealed that the majority of these patients were immature and inadequate personalities who had previously reacted to stress by producing psychogenic symptoms. In some men the sleep-wakefulness pattern was disturbed by a combination of unforeseen circumstances over which they had no control.

In each and every case psychological and environmental causes were found to be responsible for the symptoms, which were precipitated by lack of suitable employment, by uncongenial jobs, or by boredom. Excessive sleep and abnormal appetite when found in the same patient were due to two entirely different factors, and both symptoms were manifestations of neurosis.

This was perhaps well illustrated by some of the ex-prisoners of war. These men had spent long periods in camps in Germany, Italy, or the Far East. On repatriation they were given permission to draw extra rations and were also granted accumulated leave varying from three to four or more months. During furlough they ate a lot and naturally slept a good deal. There was thus a primary disturbance of the sleep-wakefulness cycle, and quantitative non-pathological hypersomnia became a daily habit.

On the expiry of their leave, instead of being released from the Forces as they had fondly hoped, they were asked to report for duty. They alleged that at the holding battalion headquarters they were made to do drills on the square; and that some of their instructors were young non-commissioned officers who had only a few months' service. The drill bored them and they resented being "ordered about" by young N.C.O.s who had never seen any active warfare. These were some of the psychological factors which helped to maintain the excessive sleep pattern.

The ordinary Army rations given to them at the holding battalion seemed to them inadequate by comparison with the double rations to which they had got accustomed while on furlough. Not all these men could easily adjust themselves to this sudden reduction in diet. Some complained of feeling "always hungry."