The Archives of Internal Medicine

Vol. XIV

DECEMBER, 1914

No. 6

CLINICAL STUDIES IN CAFFEIN *

LESTER TAYLOR, M.D.
CLEVELAND

The pharmacological action of caffein as it relates to the normal man and animal has been for many years the subject of extensive research. Its main effects on the normal cardiovascular and nervous systems are well known. Briefly stated for the purpose of this paper, this effect of caffein in moderate doses is, first, to produce a moderate rise of blood-pressure due to a stimulant action on the heart muscle (this rise is maintained in spite of a mild degree of vasodilatation); second, an increased urinary output due to circulatory changes, and third, an increased respiratory rate. The cerebral functions are stimulated and the muscle tone increased. This experimental field was reviewed and the varying results of the different investigators harmonized by Sollmann and Pilcher¹ in 1911.

With this action in mind the pharmacologists have given the drug a high therapeutic rating and it has been extensively used as a cardiac and nerve stimulant. It is one thing to inject a drug directly into the blood-stream of an animal with a normal circulatory system or again into an animal under the influence of an anesthetic and the surgical procedures necessary for the recording of blood-pressure, variations in the size of the kidney, etc.; and quite a different thing to give a drug by mouth, in the usual clinical way, where the absorption is more or less delayed and in cases in which the cardiovascular system is not intact. In one case the results may be prompt, definite, limited; in the other case they may be slow to appear, indefinite, and continued

* Submitted for publication June 23, 1914.

* From the Medical Clinic of Prof. C. F. Hoover, Lakeside Hospital and Western Reserve University.

* An abstract of this paper was read at the Philadelphia meeting of the American Society for Pharmacology and Experimental Therapeutics, December, 1913.

* This investigation was undertaken at the suggestion of the Committee on Therapeutic Research of the Council on Pharmacy and Chemistry of the American Medical Association.

1. Sollmann, T., and Pilcher, T. D.: The Actions of Caffein on the Mammalian Circulation, Jour. Pharm. and Exper. Therap., 1911, iii, 19.

in their action. In the animal the distressing symptoms caused by the drug are beyond the reach of the investigator to determine; in the sick man these assume paramount importance. With the idea of further testing the effect of caffein on the pathological circulatory system of the human being, and if possible adding to our clinical knowledge of the drug, these observations were made.

The patients chosen were all adults, the youngest 24, the oldest 56, suffering from advanced myocardial disease. In some cases the myocardial insufficiency was primary, in others secondary to a chronic nephritis or an old endocarditis. The fifteen cases reported were selected because in these cases the observations were fairly complete. In numerous other cases the loss of specimens, death, or intercurrent complications requiring the use of other therapeutic measures made the analysis of caffein action impossible. Every case showed some sign of broken compensation at the time of the experiment, and thirteen gave evidence of retained body fluid. Dyspnea was present in 14 cases; edema of the extremities in 13 cases; ascites in 10 cases; hydropericardium and hydrothorax, single or double, in 6; tender pulsating liver in 6. Other common symptoms were cough, frontal headache, weakness, dizziness and substernal pain.

All patients were kept in bed on a constant diet. Milk with the possible diuretic action of its milk-sugar was eliminated in all but one case, and here milk had been a constant factor in the diet for several days previous to the administration of the drug. No effort was made to reduce the salt intake. The fluid intake was measured and in eleven of the fifteen cases was kept constant at amounts varying in the different cases from 930 to 2,100 c.c., depending on the wish of the patient. The patient was allowed to use what water he wanted on the first day, and that amount was taken as a constant for subsequent days. The average intake was 1,200 c.c. No medication or depleting therapy of any kind was allowed for four days preceding the experiment, so that rest as a factor in restoring cardiac function might come as near as possible to a constant level.

In eight cases citrated caffein was used in doses of 10 grains, four times daily. In Case 2, in which there was no noticeable result with that dosage, it was pushed to 100 grains a day. In two cases the dose was reduced to 5 grains, three times a day. The average of the eight cases was 32.5 grains a day of the citrate, which is the equivalent of 16.25 grains of the pure caffein. In seven cases the pure alkaloid, *caffeina*, was used in doses of 3 to 5 grains, four times daily; an average of 17.7 grains per day. The drug was discontinued usually because of the appearance of unpleasant symptoms. The average use of the citrate extended over 4.8 days, that of the pure drug, 4.6 days, so that

both the dosage and the length of time during which the different preparations was used were practically the same.

Effect on the Pulse-Rate.—The pulse was taken one-half hour before and again one-half hour after the administration of the drug. The rate previous to giving the drug was taken as the gauge of a permanent drug effect, and in this series of observations showed no definite change. In six cases there was a permanent rise of five beats a minute, or 7 per cent., but in eight others there was a drop of 7 per cent., so that these variations fall well within the limits of chance disturbances. In one case an intercurrent febrile attack sent the pulse-rate up, invalidating the result. The maximum effect on the pulse-rate appeared in one-half hour and consisted of a temporary rise in every case, varying from 2 per cent. in Case 6 to 5.7 per cent. in Case 10. The average rise was 3.6 per cent. This rise, it is true, is relatively small, but in this series constant and for that reason worth noting. In none of these cases was there a tachycardia, the pulse ranging from 70 to 90. This fact combined with the relatively small temporary rise made it impossible to make any clinical comments on the fact noted in dogs that caffein causes a greater quickening in hearts which have a high rate. Certainly we may say that in this group of cases caffein has no permanent or clinical effect on the heart-rate.

Effect on the Respiratory Rate.—This was determined, as was the pulse-rate, by observations one-half hour before and after the administration of the drug, a total of eight readings a day. Even in cases with dyspnea and the relief of that symptom, the change in the rate could not be ascribed to the action of the caffein directly on the respiratory center, but rather to a secondary action through improvement of the circulation. In cases without dyspnea or in the cases in which the dyspnea had subsided, there was no effect, permanent or temporary, which could be clinically determined.

• *Effect on the Blood-Pressure.*—The pressure was measured usually at 10 a. m. with a 10 cm. cuff, Riva-Rocci, by the auscultatory method. Chart 1 gives the pressure from day to day in each case, and in Chart 2 is given the composite curve of the fifteen cases. In twelve of the cases there was a marked drop in the pressure varying from 8 mm. in Case 12 to 50 mm. in Case 15. In Case 10, in which the endocardium was mainly at fault and there was little stasis, the blood-pressure remained at 135 mm. systolic. In Case 9 a pressure of 120 rose at first to 140 under caffein, but later dropped to 112 mm. In Case 3, in which the largest dosage was used, a case of luetic myocarditis confirmed at necropsy, the pressure rose under 100 grains of caffein daily from 172 systolic and 125 diastolic to 192 systolic and 150 diastolic. In three cases the drop was between 40 and 50 mm.; in three cases

between 30 and 40; in three cases between 10 and 20, and in three cases below 10. The mean curve shows a slight drop the first day and a well-marked drop the second and third day with a gradual fall thereafter, the fall averaging about 2.5 mm. per day. That there is good clinical evidence that this drop in blood-pressure is due partly at least

Chart 1.—Individual curve of blood-pressure (o---o---o—o—o) and diuretic coefficient and after the drug. The base line corresponds to a diuretic coefficient (output of urine divided by sure of 110 and diuretic coefficient of 1.1, etc. The dosage refers to grains per day of either citrated

to a peripheral dilatation of the vessels will be discussed later. From the charts then we may conclude that the final effect of caffeine on the blood-pressure is to produce a depression, although in a few cases this may be preceded by a temporary rise on the first day. The fall is apt to continue after the administration is stopped.

subsides. This return of the urine flow toward the normal is doubtless due to the smaller amount of disposable fluid, as the edema disappears. In all fifteen of the cases there was some rise on the second or third day, although in three of the cases it was not sufficient to be of any clinical importance. In two of these twelve cases the urine output equaled or excelled the fluid intake. It will be noted from the individual curves that while the ascent of the curve is not so marked on the third and fourth day, nevertheless the cases that respond most favorably to the drug show their greatest activity at that time. The less favorable cases show their activity on the first and second day and subside again. In two cases the stopping of the drug produced a secondary rise. In three of the four cases with their maximum on the fourth day the diuretic coefficient was 2.1, 2.7 and 2.8.

Chart 2.—Mean curves (compiled from the fifteen cases) of diuretic coefficient body, weight and blood-pressure. The base line corresponds to the level when caffeine was started. Each square corresponds to a change of 0.1 in the diuretic coefficient, of 2.5 mm. of blood-pressure, and of 2.5 pounds of body weight.

When the mean curves of the blood-pressure and the diuretic coefficient are superimposed, the relation of these two factors seems at least suggestive, the diuresis varying inversely as the pressure. I would recall here the work of Loewi, who demonstrated that diuresis under caffeine in the lower animals was due largely to a dilatation of the renal vessels. That there is also a general vasomotor relaxation has been demonstrated, although the cardiac action of caffeine is usually regarded as sufficient to maintain or even elevate the blood-pressure. That caffeine increases the tone of the blood-vessels is a popular therapeutic idea which animal experiment and clinical observation deny. Taking the cases singly, one finds that the day with the largest drop in the pressure there will also appear the largest urine output. And through-

out, those cases which showed the greatest elimination of body fluid also showed the greatest general drop in blood-pressure. Of special interest was Case 14 in Chart 1. Here are shown very marked oscillations in the curve, the maximum diuretic coefficient appearing at four-day intervals, and associated with a marked drop in blood-pressure. A drop in the systolic pressure from 160 mm. to 130 mm. would be associated with a jump in the diuretic coefficient. This action was probably due to a spasmodic hypertonus, and the relief of the hypertonus could very well be absolutely independent of the caffeine, although these blood-pressure changes did not appear until the caffeine was begun. In the other cases, however, we did not see such marked action from the caffeine on the blood-pressure. It can hardly be explained by the action of caffeine on the vasomotor centers, because we find that after caffeine the normal irritability is reduced, contrary to

Chart 3.—Comparison of caffeine and theobromin sodium salicylate. Mean curve of diuretic coefficient from five patients (3, 6, 7, 9, 13), on whom both drugs were used under similar conditions.

what we might expect from its other cerebral action. We feel, therefore, that the clinical diuretic action of caffeine is the result of reduced pressure and vasodilatation.

Effect on the Body Weight.—As is to be expected, the weight decreases with the loss of fluid by the diuresis, so that the curve of the body weight (Chart 2) will be seen to vary inversely as the curve of the diuretic coefficient. These individual curves could not be included with the blood-pressure and the diuretic coefficient without complicating the curves so that they would be unintelligible. Only the composite curve is shown here. The weight of the patient's stool was considered, and in these curves we can tell when the loss of weight is due to the loss of body fluid. The first day shows a small drop which continues steadily, the largest drop occurring in cases in which the

action extended over six or eight days. Three cases, Nos. 6, 9 and 11, showed a small gain in weight up to 4 pounds with increased retention of body fluid, the other cases showing a loss varying from two to twenty pounds consistent with their urine output. Chart 2 shows the relation of the composite curves of the blood-pressure, diuretic coefficient and the body weight after caffein administration and with the four days' control.

Unpleasant Symptoms.—One of the most constant findings was the unpleasant symptoms from the drug. The caffein was given in capsules or powders by mouth, in 3 ounces of water, rather than hypodermatically, in order that its use might correspond to the ordinary clinical administration. These effects were mainly nervous and gastric. In thirteen of the fifteen cases there was discomfort shown from the

Chart 4.—Comparison of several drugs on same patient (Case 7). The upper curve is the blood-pressure; the lower, the diuretic coefficient. The doses are grains per day.

drug. Eight patients were unable to sleep; seven complained of a vague uneasiness, a sense of restlessness; seven had nausea; five vomiting; four headache; two could not eat, and one besides being unable to eat or sleep insisted that the medicine gave him a pain in the side, the cause of which was not determined. The doses used were full doses, it is true, but no larger than necessary to secure results, and when they were reduced below the point where they gave nervous phenomena their cardiac value had disappeared.

Clinical Efficiency.—Grouping the cases according to their clinical action, the drug has been credited with excellent results, moderate or none, according as it has relieved the subjective symptoms of cardiac origin, caused a diuresis or removed the objective signs. Of the fifteen cases the results were excellent in eight; moderate in four, and there was no result in three. In one of the cases where there was

no result, the vomiting and loss of sleep even on small doses more than balanced any possible good that the drug could have done. All the cases with limited results showed the nervous signs, so the absorption of the drug was assured.

Comparison with Theobromin Sodium Salicylate.—In five of these cases a second admission to the hospital or a return of symptoms while they were still in the institution made it possible to try the comparative therapy of theobromin sodium salicylate under the same conditions and on the same heart on which the caffein action had been tested. Two charts are shown. One, Chart 3, represents two composite curves of these five cases. They show the mean curves of the caffein and theobromin sodium salicylate action on the diuretic coefficient, and are self-explanatory. The other, Chart 4, represents the relative effects of various drugs on the blood-pressure and diuresis in the same case, an old myocarditis. This chart is in accord with the other charts and our clinical experience in demonstrating that, while the action of caffein as a cardiac diuretic may be proved, still it is often of no clinical importance and is very much weaker than the other diuretics.

Our conclusions in regard to theobromin sodium salicylate are that its action on the urinary outflow is more prompt than that of caffein and the diuresis is larger. One can usually tell in twenty-four hours, in a given case, whether theobromin sodium salicylate will act or not; while with caffein the third or fourth day is more apt to show results. The theobromin sodium salicylate action is equally well sustained and usually at a higher level than the caffein. Where caffein has a depressing effect on the vasomotor system and lowers the blood-pressure, theobromin sodium salicylate first elevates the pressure and then later lowers it. The dosage of theobromin sodium salicylate we have found to play an important part in its action. As shown in Chart 4, a dosage of 30 grains daily, even though combined with digitalis, gave but little result; 40 grains daily gave a moderate diuresis, but a vigorous and prompt diuresis is the result of pushing the dose to 80 grains a day. In the chart this fact may be seen at two different points. This has been a frequent clinical experience, so that we regard 80 grains a day as a normal clinical dose. Patients will tolerate this dose easily, and this is an important practical factor in choosing a drug. Not only is the theobromin sodium salicylate action prompter, much stronger and equally well sustained, but we have found none of the gastric and nerve disturbances attendant on caffein. It is useless to give theobromin sodium salicylate in a given case and wait any length of time for its action to appear. In this group of cases with myocardial edema, experience with both drugs demonstrates the decided superiority of theobromin sodium salicylate over caffein. The relative value

of the two drugs in arterial disease, cerebral and coronary sclerosis, is of course an entirely different problem.

Effective Dosage of Caffein.—In cases with edema, the diuretic effect of the drug may be safely taken as a sign of an improved mass movement of blood, which is the result we desire. From this point of view it is evident in this series that the small doses advocated by Romberg are not adequate. The best results were obtained in Cases 4, 5, 6, 8 and 14 with full doses. A good result was also obtained in Case 13 with a smaller dose, but even this dose, from 10 to 15 grains daily of the pure caffein, is much larger than that advocated by Romberg, who uses 2 grains for three doses. Inversely, in the cases with the smaller dose, Cases 2, 9 and 11, there was little clinical value from the drug. By administration by mouth the larger doses must be used to be efficient and almost always at the risk of unpleasant symptoms. The doses were often pushed to the limit of the patient's comfort, but there was no evidence that such doses produced an oliguria or a reversal of the vascular action. The hypodermic use of caffein in acute pulmonary edema and other acute heart conditions as a prompt cardiac stimulant will be taken up in another paper, in which I shall also present findings as to the nature of this caffein diuresis and the action of the drug on renal anasarca. In this series the hypodermic method was not employed, because even in hospital practice so many repeated injections have their disadvantages.

SUMMARY

In myocardial insufficiency with retained body fluid, caffein causes:

1. A moderate increase in the urine output with a proportional loss of body weight. This increase reaches its maximum on the fourth day.
2. A drop in both the systolic and diastolic blood-pressures which may stand in a causal relation to the diuretic coefficient, contrary to the usual teaching.
3. A slight (3.6 per cent.) temporary rise in the pulse-rate, but no permanent change in either the pulse or respiratory rate.
4. A moderate relief of the cardiac symptoms.
5. The constant appearance of distressing nervous and gastric symptoms.

The clinical diuretic action of caffein may be better performed by large doses of theobromin sodium salicylate without the unpleasant side effects.

This preliminary report is presented with a feeling of deep gratitude to Dr. C. F. Hoover and Dr. Torald Sollmann for their generosity with material and constant valuable suggestions in carrying on this work.