Assay of Anti-Anginal Agents

I. A Curve Analysis with Multiple Control Periods

By Seymour L. Cole, M.D., Harry Kaye, M.D., and George C. Griffith, M.D.

The measure of an anti-anginal agent is its ability to decrease chest pain. Because of the subjective character of pain, extreme care is necessary in choosing patients upon whom anti-anginal medication is to be tested. We have used the double-blind technic and an initial control period to neutralize the many extraneous mental and physical factors, such as bias or the patient-physician relationship itself, that might interfere with an accurate appraisal. This study shows, in addition, that proper evaluation of an anti-anginal agent requires that its effect be measured against multiple control periods without medication throughout the various phases of angina pectoris.

OPINIONS concerning the efficacy of each of the various medical agents in the continuous treatment of angina pectoris have ranged from the enthusiastic to the negative. In an attempt to determine the place of anti-anginal agents in the management of this symptom-complex and to resolve these recurrent discrepancies, 4 drugs were tested: triethanolamine trinitrate (Metamine), calcium theophyllinate (Calphyllin), pentaerythritol tetranitrate (Peritrate), and chlorpromazine (Thorazine).*

PROCEDURE

An angina study group was formed to which patients with angina pectoris were referred from the cardiac outpatient clinic of the Los Angeles County Hospital. The group met with patients at weekly intervals over a 2-year period. At the initial visit each patient was carefully evaluated as to the presence of angina pectoris on the basis of coronary artery disease—from history, physical examination, electrocardiograms, and other laboratory procedures. At each follow-up visit patients were questioned concerning the course of the disease and the effect of medication they were taking; they were weighed, their blood pressures were taken, and heart and lungs were examined. Every patient was instructed in keeping a daily record sheet of the number, frequency, duration, and severity of anginal attacks, together with the number of nitroglycerin tablets taken. At each visit these sheets were reviewed, and the patients were questioned concerning emotional upsets, concurrent illness, changes in rest or activity, and any other factors that might be expected to affect the course of angina pectoris. All pertinent facts, together with patient's opinions as to the efficacy of medication or absence of medication during the preceding period, were then assembled on a master chart.

A control method was employed, in that each patient had repeated periods during which he received, in random succession, (1) no anti-anginal medication other than nitroglycerin; (2) pills containing the active drug under study, plus nitroglycerin as needed; (3) blank pills, identical in appearance with the drug, plus nitroglycerin as needed. Neither physicians nor patients knew whether active drug or placebo was being given. Frequent control periods without medication were obtained. Electrocardiograms were taken initially and following each successive trial of drug and of identical placebo.

A continuous graph was constructed from each patient's daily chart to show the average daily number of chest pains and nitroglycerin tablets taken per week per period for the entire study, and the multiple successive control periods without anti-anginal medication (other than nitroglycerin).

A patient was considered to be improved when the severity, duration, and frequency of anginal attacks were lessened and when nitroglycerin intake was decreased. In addition, a drug was considered to be effective when a patient reported a definite sustained improvement from it or asked for the drug to be continued past the period of its scheduled use.

Selection of Patients

Less than one-fourth of the patients referred to the angina study group from the cardiac outpatient clinic of the Los Angeles County Hospital proved suitable subjects for the evaluation of anti-anginal agents. Principal factors responsible for exclusion of the majority of patients included chest pains from

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FIG. 1. Ski curve showing progressive decrease in chest pain frequency followed by prolonged plateau of lesser pain frequency (the post-rapport period). MET = Metamine (2 mg.), CAL = Calphyllin (0.5 Gm.), PER = Peritrate (10 mg.), TH = Thorazine, Pmet = Metamine placebo, Pcal = Calphyllin placebo, P per = Peritrate placebo (3 to 8) = number of tablets daily. (Notations are the same for figures 1-6).

FIG. 2. Ski curve complicated by emotional stress in the post-rapport period.

other sources—cervical arthritis, peptic ulcer, gallbladder disease, or diaphragmatic hernia, to mention a few—which tended to obscure the patients' anginal attacks; a psychogenic overlay of anxiety of such magnitude that every minor ache or chest pain was construed as an anginal attack; inability or unwillingness to keep the detailed records necessary; and too few attacks.

A patient's unsuitability was not always immediately apparent. Seventeen patients were eliminated only after the study had already been under way for some weeks. For example, one patient persisted in listing the same number of pains each day although, on close questioning, she was found to experience marked daily variation in frequency of attacks. A second patient claimed to have "175 to 250 separate severe pains in the chest each day..." unverified, naturally, by other members of the family. A third patient, whose angina apparently was severe enough to require him to take 12 to 15 tablets of nitroglycerin each day, proved able to go without a single tablet for a period of 3 weeks after his supply of tablets was exhausted. Some patients eventually were found to have too few attacks for statistical study; others found it impossible to attend the clinic regularly. One patient died of myocardial infarction.

The remaining 24 patients, 13 men (41 to 79 years old) and 11 women (48 to 89 years old) formed the group studied. Two men and 4 women had a history of myocardial infarction, 8 (5 women and 3 men) had hypertension, and 1 woman had syphilitic aortic insufficiency and aortic aneurysm.

RESULTS

Curves

Graphs of the average number of daily anginal attacks per week yielded curves that usually paralleled graphs of the number of nitroglycerin tablets taken, although the latter were more variable. On some occasions the attack was too short or mild for the patient to take a nitroglycerin tablet; on other occasions the patient would take more than one tablet during an attack. The number of nitroglycerin tablets taken by 1 patient increased suddenly although the number of attacks remained constant because that patient became convinced he might prevent the attack if he took nitroglycerin prophylactically. Similarly, nitroglycerin intake of another patient increased when he found he was permitted to take more nitroglycerin tablets than a (self-imposed) restricted daily number. As "pain" curves generally paralleled nitroglycerin intake curves, and the latter were more variable, only the "pain" curves will be taken into consideration. Since patients had difficulty in evaluating the severity and duration of pain, only the frequency of pains has been plotted.

Analysis of the continuous curves of pain frequency reveals 6 main types. The first curve (found in 14 of the 24 patients) resembles a ski in shape—with an initial downward slope representing improvement regardless of succession of drug, placebo, or no medication, followed by a straight line or plateau of longer duration (figs. 1-3).

The second curve (found in one third of the patients) is a straight line, showing no marked deviation regardless of drug, placebo, or period.
of no medication (fig. 4). The third (3 cases), a modification of the second, is a straight line with minor fluctuations, without apparent cause or correlation with drug, placebo, or period of no medication (fig. 5).

The fourth curve (3 cases) demonstrates a hump coincident with a period of emotional strain (fig. 2) or concomitant illness that caused a temporary increase in frequency of attacks of pain (fig. 3). Increasing severity, due to general deterioration of the patient's condition or following myocardial infarction, caused the hump to become an ascending slope (the fifth type seen in 3 cases, fig. 6).

Sixth, (1 case) is a dip in the curve representing a decrease in the frequency of chest pains due to drug therapy—a decrease more pronounced than the decrease following placebo administration or periods without medication (fig. 3).

The initial downward slope of the ski curve ranged from 5 to 21 weeks and averaged 11 weeks.

An average of 3 control periods per patient was obtained: the range was 2 to 6 control periods in the majority of the patients who were conscientious in clinic attendance. The maximum number of pains during a control period (period without anti-anginal medication) was 29; the minimum, 0—during a period of complete remission. For the individual patient, a maximum variation of 12 episodes of severe pain was reported during control periods; on the average, variation among control periods was 6 pains.

**THE DRUGS**

**Metamine**

Metamine, in 2-mg. tablets, was prescribed for 24 patients, to be taken after meals and before bedtime in daily doses ranging from 6 to 16 mg. For periods averaging 5 weeks, 2 patients took 1 tablet 3 times a day; 20 patients
took 1 tablet 4 times a day; and 12, some of whom had been on the lesser dosage, took 2 tablets 4 times a day. Increase in dosage employed was not found to cause a concomitant decrease in attacks of chest pain.

Comparison of Metamine and its placebo with only the initial control period without medication made it appear that 9 patients were improved by Metamine; 2 were improved by the placebo; 2 were improved by both Metamine and by the placebo; 11 patients were not improved by Metamine or the placebo. When periods of drug and placebo medication were analyzed on the curve against multiple successive periods of no medication, however, the number of pains and number of nitroglycerin tablets found to be equally as low in periods with no medication for all patients but the few who had preliminary but no successive control periods without medication. One patient complained of nausea and headache following the drug—not severe enough to make him discontinue the active drug; none of the patients experienced side effects from the placebo. No patient voluntarily asked for Metamine to be continued beyond the scheduled time. Serial electrocardiograms showed no changes that could not be explained by the varying course of coronary disease. No significant changes in pulse or blood pressure or weight occurred.

Calphyllin

Calphyllin, in tablets of 0.5 Gm., was given in total doses ranging from 1.5 Gm. to 2.0 Gm. Seventeen patients took Calphyllin in doses of 0.5 Gm. 3 times a day after meals or 4 times a day—the last dose before bedtime.

Comparison of Calphyllin and its placebo, with only the first control period without medication, appeared to show that 3 patients were improved by Calphyllin; 2 were improved by the placebo; 1 was improved by either Calphyllin or the placebo; 11 were not improved by either Calphyllin or the placebo. When periods of drug and placebo medication were contrasted with successive periods without medication, however, the frequency of anginal pains and numbers of nitroglycerin tablets taken were just as low in periods without medication. Six patients had gastrointestinal complaints, consisting of nausea, heartburn, abdominal burning and cramps, and constipation. Three patients had similar complaints while taking the placebo. One patient stopped the medication because of tachycardia and palpitation. The others were induced to continue medication throughout the period of study in spite of the side effects. No patient requested Calphyllin past the test period. No significant changes in electrocardiograms, blood pressures, and pulse rates were noted.

Peritrate

Peritrate, in 10-mg. tablets, was prescribed for 14 patients before meals and at bedtime in daily doses ranging from 40 to 80 mg. Seven of these patients received 10 mg. 4 times a day, and for periods averaging 7 weeks all 14 patients took 20 mg. 4 times a day. In addition 2 of the patients received Peritrate from outside sources for brief intervals extraneous to the study.

From comparison of Peritrate with its placebo and with only the initial control period without medication, it appeared that 6 patients were improved by Peritrate; 1 patient was improved by the placebo; 1 patient was improved by both Peritrate and the placebo, and 6 patients were not improved by either Peritrate or the placebo. When periods of drug and placebo were compared on the curve with successive periods of no medication, only 1 patient still showed greater improvement while receiving Peritrate. Another patient reported a definite increase in frequency of chest pains when she ran out of Peritrate. Of the 2 patients who had received Peritrate from extraneous sources, although both remembered previous benefit, only 1 was improved during the administration of Peritrate in this study. Seven of the patients on the larger dose of Peritrate, and 3 on the placebo had headaches and minor gastrointestinal discomfort, not severe enough to require cessation of medication. No electrocardiographic changes occurred that could not be explained by the usual course of coronary disease; no significant changes in weight, pulse or blood pressure were noted.

Thorazine

Thorazine was given to 4 patients in doses ranging from 10 mg. to 50 mg. 4 times a day as
a pilot study. Temporary improvement was noted on 40 mg. a day in 2 patients. When improvement could not be maintained even though the dose was quintupled, further investigation with Thorazine employing multiple control periods was not attempted.

**DISCUSSION**

Assay of an anti-anginal agent is the measurement of a completely subjective sensation—the decrease in frequency and severity of chest pain. Studies have shown pain to involve not only physical perception but also a psychologic reaction. The level of pain perception normally is fairly uniform from individual to individual, but persons vary greatly in their reaction to pain. Since the effectiveness of anti-anginal agent is based on a cooperative patient's report of his reactions, the many factors that condition these reactions must be taken into consideration before a valid evaluation of the agent can be made.

Effects of these factors on the capricious course of angina pectoris is illustrated in the continuous curves of pain frequency. Comparison of multiple control periods without drugs at successive stages along the curves shows spontaneous fluctuations and demonstrates great variation in frequency of anginal attacks in response to mental, emotional, and physical stimuli.

A good example is the initial downward slope of the ski curve that occurred in over 50 per cent of the subjects during the first 3 months of observation, regardless of the random succession of drug, placebo, or period without medication. The decrease in frequency of chest pain was probably due to the fact that the patients were taken from a general cardiac clinic and placed in a select group for special attention. The establishment of exceptionally good psychologic rapport between doctor and patient, and the attendant ceremony of drug research are considered primary causes for improvement during this period. This observation agrees with that of Master and co-workers who stated that any new type of therapy may bring relief from attacks of chest pain for a few weeks. The remainder of the ski curve was usually a level plateau in which the number of pains in control periods almost always was much less than at the beginning of the study. Without these control periods (without medication) credit would be given to any medication that was being administered at the time.

The effect of physical disease or emotional disturbance was evidenced by a temporary hump in the plateau or straight line curves. On 3 occasions the hump became an ascending slope when the patient's general condition worsened, following myocardial infarction or concomitant illness. These findings bear out the statements of Gold and associates, that when a patient declares that pain has diminished during medication, improvement may be due to specific action of the drug, or to any of a number of factors—change in weather, change of occupation or in amount of work performed, change in eating habits, increase in amount of rest, relief of constipation, alleviation of emotional stress, and improvement in financial or domestic affairs, to mention but a few. The action of drugs used in this study has a relatively minor effect. In only 1 case in this series did a definite dip occur in the curve showing a decreased number of anginal attacks during period of active drug administration as compared with placebo administration and periods without medication.

Angina pectoris is a variable subjective manifestation with little consistent quantitative relation to the underlying coronary disease, and little correlation with electrocardiographic changes under the stress of exercise. Silber and Katz emphasized that angina pectoris is pain and, in this sense, must be analyzed in terms of the physiology of sensation, quite apart from factors having to do with coronary flow. As they state, "it cannot be shown that there is a high correlation between the ability of a drug to prevent electrocardiographic changes under stress and to prevent anginal pain." To find patients with coronary disease on whom to test coronary vasodilators, Russek and associates spent 4 years and screened 3,000 patients before they found 52 individuals with a relatively constant positive response to a given amount of exercise. Batterman, commenting on this work, asserted that although some subjects have a sensitive electrocardiographic configuration that may or may not respond to certain drugs, electrocardio-
graphic response is not a valid measure of the effectiveness of the drug in the treatment of angina pectoris, a subjective pain sensation.

Since Heberden's concise classic, it has been clear that attacks of angina pectoris vary greatly in intensity and frequency not only in different individuals but in the same individual from time to time. Periods of marked improvement to complete remission for a few days extending to several weeks have been observed. Any drug administered at that time, active or inert, would get credit for the improvement.

In addition to its pharmacologic action, every drug has a placebo effect that is derived from the urgent need of patients for relief and from the communication of the physician's enthusiasm (positive suggestion that the drug will help). Thus the total drug effect is equal to its active effect plus its placebo effect. Placebos have been shown by Evans and Hoyle to relieve the pain of angina pectoris satisfactorily in 38 per cent of their patients. Beecher collected 15 studies involving over 1,000 patients, in which placebos were found to have a degree of effectiveness measuring between 35.2 plus or minus 2.2 per cent.

Greiner and co-workers showed the manner in which the double-blind test can neutralize the power of the influence of suggestion that otherwise might confuse the results in a study of drug effect on cardiac pain. The importance of this technic in bypassing the bias of the physician and the suggestibility of the patient in the evaluation of an anti-anginal agent is illustrated by Gold in discussion of the Egyptian drug, khellin. "When a physician knew which was drug and which was placebo, a large number of patients appeared to obtain relief of cardiac pain.... When the study was repeated in the same group of patients but neither physicians or patients were aware of the identity of the agents, then the placebo and khellin could not be distinguished with respect to the effect on cardiac pain." Another group of investigators similarly had to re-appraise their experience with khellin and papaverine in angina when they retested these drugs employing the double-blind technic.

In addition to the double-blind test, to evaluate properly an anti-anginal agent in a symptom-complex as variable as angina pectoris, it must be measured against multiple control periods without anti-anginal medication during each of its phases. Table I shows that to measure the effect of a drug by the reduction of the number of attacks as compared with an initial control period alone is not sufficient. Comparison of drug and placebo must be made during and after the initial period of improvement, which may last more than 3 months, and during periods of physical and mental stress and strain.

Palmer and Ramsay in a preliminary study, and Fuller and Kassel at a later date, reported that Metamine was much more effective than placebos in the prevention of anginal pain. In neither of these studies were multiple successive periods without medication provided as controls, nor was the double-blind technic employed. Silber and Katz and Friedberg failed to find Metamine effective in the treatment of anginal pain. Results in the present series agree with those of the last mentioned authors and of Friend and co-workers, who also found Metamine to be ineffective when tested with the double-blind technic against 2 controls.

Gold's group traced the use of xanthine derivatives back to 1895 and commented that the beneficial results in percentages up to 80 per cent were from reports of clinical experiences rather than controlled investigations. His experience agreed with that of Evans and Hoyle, who found that when xanthishes were
tested against placebo controls, they did not show themselves to be worthy even of trial in the routine treatment of cardiac pain. Waxler and associates10 believed that the difficulty with xanthenes was that their dosage could not be increased enough for a beneficial response without marked gastrointestinal disturbance. Calphyllin showed no improvement over its identical placebo in this series and did not substantiate hope that it might be freer of side effects than its predecessors in the xanthine series.

Peritrate was found by Winsor and Humphreys8 to be effective in preventing anginal attacks; more effective than Metamine, by Winsor and Scott,21 but neither multiple successive control periods nor the double-blind technic was employed in these studies. Russek and associates22 believed that Peritrate protected selected patients with coronary artery disease from electrocardiographic changes produced by an exercise test. They did not demonstrate, however, that Peritrate decreased the frequency of attacks of angina pectoris, a completely subjective manifestation. Perlman23 found Peritrate to be partially effective some of the time. Salans, Silber, and Katz,24 Friedberg,17 and Talley, Beard, and Doherty25 found Peritrate ineffective in the treatment of cardiac pain. Although, in the doses used in the present series, Peritrate reportedly had decreased the frequency of anginal attacks in 2 persons when they had received Peritrate previously from extraneous sources, only 1 of the 2 obtained relief in the present series, the other did not.

Perhaps Peritrate would have been more effective in higher dosage than the 80-mg. total daily amount used in this series. Weitzman26 found that raising the dose from 180 to 240 mg. a day gave relief in only 2 of 9 cases, however; in 3 cases, doses of 180 mg. caused undesirable side effects, enough to necessitate withholding the drug.

In the doses used in this study, none of the active drugs tested were distinguishable from placebos identical in appearance in ability to prevent chest pain, nor did the patients consistently prefer any drug for its beneficial effects or request its use beyond the prescribed period.

### Summary

To assay anti-anginal agents, continuous graphs were constructed from the average daily attacks of pains per week of patients with angina pectoris during periods, in random succession, of active drug, identical placebo, and no anti-anginal medication (other than nitroglycerin), utilizing the double-blind technic.

Multiple control periods without anti-anginal medication, spaced in succession along the curves of frequency of chest pain, illustrated the naturally capricious course of angina pectoris.

Analysis revealed 6 kinds of curves.

1. Regardless of the random succession of active drug, placebo, or no medication. Over 50 per cent of the curves resembled a ski: an initial downward slope of decreased frequency of attacks, representing improvement during the first 11 weeks on the average, was followed by a long plateau that usually remained at this lower level of pain frequency. The initial period of improvement was attributed to the psychotherapeutic effect of increased attention and solicitous care inherent in a research program as compared with routine clinic care. After good rapport was reached between physician and patient, the curves leveled off at a plateau of lower frequency of anginal attacks.

2. Approximately 30 per cent of the curves resembled a straight line, unaffected by active drug, placebo, or period without medication.

3. Three of the straight line curves had minor fluctuations that were without apparent explanation.

4. Two curves showed humps of temporarily increased frequency of anginal attacks that coincided with and lasted as long as an emotional upheaval in one instance and an episode of abdominal pain in the other.

5. Three curves showed a steady ascending slope of increased frequency of chest pain, that followed myocardial infarction in one instance, and general deterioration of the patient's condition in the others.

6. In 1 instance there was a dip showing a decrease in attacks of chest pain during a period of active drug therapy (Peritrate) as compared with periods of placebo and no medication.
None of the drugs used, Metamine, Calphyl-lin or Peritrate, consistently could be distin-
guished from its placebo by doctors or pa-
tients on the basis of its effectiveness in
decreasing chest pain.

Conclusions

The curve analysis with multiple control
periods showed that angina pectoris is improved
by the psychotherapy inherent in a solicitous
doctor-patient relationship, adversely affected
by mental and physical stresses and strains,
and is relatively unaffected by the anti-anginal
agents as used in this study.

To evaluate properly an anti-anginal agent
in a symptom-complex as variable as angina
pectoris, the agent should be measured against
multiple successive control periods without
medication representing all phases of frequency
of attacks of chest pain. An assay against only
an initial control period is not sufficient. An
effective agent should decrease the frequency of
anginal attacks in all phases except during
complete remission.

SUMMARIO IN INTERLINGUA

Pro essayar agentes anti-anginal, continue
graphicos esseva construite ex le numeros
medie de attacos diurne per septimana ocor-
rrente in patientes con angina de pectore durante
periodos (de successio variate) de cursos de
drogas active, de cursos de identic medicationes
fictitie, e de nulle medication anti-anginal
(in ultra de nitroglycerina). Le identitate del
medication administrate esseva incognoscite al
patiente e al personal.

Le periodos de controlo, sin medication anti-
anginal, che esseva inserite a intervallos fre-
quente in le curvas del frequentias de dolores
thoracic illustra le naturalmente capriciose
curso de angina de pectore.

Le analyse del curvas revelava 6 typos
differente.

1. Sin reguardo al modo de successio del
periodos de droga active, droga fictitie, e nulle
droga, plus que 50 pro cento del curvas pre-
sentava le apparentia de un ski. In illos, un
descendita initial in le frequentia del attacos—
reflectente un melioration durante un periodo
medie de 15 septimana—esseva sequite per un
longe plateau de reducette frequentias del
doires que se manteneva usualmente a iste
nivello. Le periodo initial de melioration esseva
attribuite al effecto psychotherapeutic del
augmento de attention e sollicitude inherent
in un programma de recerca in comparison con
le routine normal del clinica. Post que un re-
tion satisfacente esseva establite inter medico
e patiente, le curvas se applattava in un plateau
de plus basse frequentias del attacos anginal.

2. Circa 30 pro cento del curvas esseva lineas
plus o minus directe, non afficite per droga
active, droga fictitie, o absentia de medication.

3. Tres del curvas linear mostrava minor
fluctuationes pro que nulle apparente explica-
zione esseva trovate.

4. Due curvas exhibiva gibbos de augmento
temporari del frequentia de attacos anginal.
Istos coincideva con un excitement emotional
in un del casos e con un episodio de dolores ab-
dominal in le altere.

5. Tres curvas mostrava un ascendita con-
tinue, reflectente un augmento del frequentia
de dolores thoracic post infarcimento myocar-
dial in un del casos e post un deterioration
general del condition del patientes in le altere
duo casos.

6. In un caso, le curva mostrava un decli-
vitate reflectente un reduction del frequentia
del attacos de dolores thoracic durante un
periodo a droga active (Peritrato) in compar-
ation con periodos de medication fictitie e de
nulle medication del toto.

Le drogas usate esseva Metamina, Calphyl-
lina, o Peritrato. Nulle del illos esseva regular-
mente distinguibile ab le correspondente medi-
cation fictitie per le medico o le patientes
super le base de su efficacia in reduce le dolores
thoracic.

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Introduction of a swab of cotton impregnated with alcohol deep into both nasal passages caused immediate return of consciousness and acceleration of the ventricular rate in 6 instances of syncope due to A-V block. Improvement of A-V conduction due to reflex sympathetic stimulation is considered responsible.

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SEYMOUR L. COLE, HARRY KAYE and GEORGE C. GRIFFITH

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