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Evaluation of carisoprodol and phenyramidol for addictiveness

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Carisoprodol (N-isopropyl-2-methyl-2-propyl-1,3-propanediol dicarbamate) is closely related to meprobamate in chemical structure (1). It is a centrally acting skeletal "muscle relaxant", and is said to be particularly effective in releasing decerebrate rigidity (1). In experimental animals it produces high voltage, low frequency brainwave patterns and blocks electroencephalographic activation (1). It is unique in that it is ineffective as an analgesic by nociceptive or withdrawal reflex tests, but it is effective in counteracting pain produced by injection of silver nitrate into the joints of rats. That it may affect the central perception of certain forms of pain is suggested by behaviour of a dog subjected to painful stimulation of an extremity. The animal would withdraw the limb promptly in response to painful stimulus, but would not show dilatation of pupil usually noticed in response to pain (1). Evidence has also been provided that carisoprodol may elevate the pain threshold in man using (*a*) high frequency electronic stimulation to the tooth (Margolin, 2) and (*b*) an ultrasonic stimulus to induce deep, aching pain to the hand (Holliday & Dille, 2).

Phenyramidol (2-[Beta-hydroxyphenethylamino] pyridine) is also a CNS acting muscle relaxant, but in contradistinction to carisoprodol, it is effective as an analgesic by orthodox withdrawal reflex tests, and its potency in animals is comparable to that of codeine (12).

Both compounds are being marketed as muscle relaxants, effective in the relief of pain due to muscle spasms (11, 2). Since both compounds represent new structural departures for analgesics, experiments were carried out at the Addiction Research Center to ascertain if either possessed morphine-like addictive qualities in man.

General methods

The subjects used in these studies were healthy adult negro or white males serving sentences for violation of state or federal narcotic laws, who volunteered for the experiments. All were former opiate addicts. Since both drugs are being marketed for clinical use by the oral route, and since addicts would have difficulty extracting these drugs for injection from the inert ingredients with which they are mixed, they were evaluated orally only. The tests employed to ascertain addictiveness were:

1. Administration of single doses to non-tolerant subjects for the detection of morphine-like effects. This was evaluated by means of the single dose opiate questionnaires [patients' and observers' ratings (7)].

2. Twenty-four-hour substitution of these drugs for morphine in patients addicted to morphine, to ascertain their effectiveness in preventing symptoms of abstinence from morphine (6).

3. "Direct addiction", which involves administration of these drugs in progressively increasing doses as tolerated for 18 days (5) and/or stabilization on the maximum dosage attained for an additional 36 to 43 days, and abrupt withdrawal of the drugs to ascertain whether physical dependence develops after either 18 or 54 days of chronic administration.

Other tests and specific details will be described under each experiment.

Part I. — Carisoprodol

1. *Effect of Single Oral Doses in Non-addicted Patients*

Methods. — Single doses of carisoprodol were administered orally in capsules to fasting, non-tolerant addicts at 8.30 a.m., and observations were carried out at hourly intervals for six hours, using the single-dose opiate questionnaires (patients' and observers' ratings).

Results. — Preliminary experiments indicated that doses below 1,000 mg induced no significant subjective effects, but with higher doses certain effects were demonstrated, as shown in table 1. It was not, however, until a dose of 2,000 mg

TABLE 1

Effects of single oral doses of carisoprodol (patient ratings)

Number of patients	Dose (mg)	Principal effects
4	1 050	3 – "blank" 1 – tranquillizer
4	1 200	3 – "blank" 1 – relaxed
4	1 600	2 – "blank" 1 – "dope" (2 of 6 responses)
5	2 000	2 – "dope" 3 – barbiturates
15	2 500	1 – "dope" (2 of 6 responses) 6 – barbiturates 3 – "blank" 1 – benzedrine 4 – miscellaneous 5 – sleepy

was given that effects were consistently observed. With 2,500 mg of carisoprodol, evaluated in 15 tests, only one of 15 patients identified it as being "dope" (opiate), and this patient identified it as such on only two of six observations. The predominate effects subjectively and objectively were similar to those of a barbiturate or alcohol, and not similar to those of an opiate. In contrast to patients intoxicated with barbiturates and alcohol, none of the patients who received large doses of carisoprodol were obstreperous, belligerent, silly or difficult to manage. One or two hours after 2,500 mg of carisoprodol, most of the subjects became quite sleepy, some profoundly so, and were difficult to arouse. They were somewhat confused when awakened, but did not show as much dysarthria as one might anticipate from an equivalent hypnotic dose of barbiturates. All patients thus affected, however, were moderately ataxic. These effects disappeared almost completely in six hours. Carisoprodol, even in the highest doses, did not induce pupillary constriction.

2. *Twenty-four-hour Substitution of Carisoprodol for Morphine*

Methods. — 3,600 to 4,800 mg of carisoprodol (divided into three equal oral doses) was substituted for morphine in 6 and 3 patients respectively. All patients receiving morphine were stabilized on 240 mg of subcutaneous morphine sulfate daily. The study was controlled in other tests, negatively, by substitution of a placebo for morphine, and positively, by continuing the customary dose of morphine in the same subjects. Observations for intensity of abstinence were made hourly from the 11th through the 24th hour of abstinence (6, 3). Since carisoprodol seemed to be barbiturate-like in many respects, the study was also controlled by substituting intramuscular pentobarbital in an average dose of 1.11 grammes divided among five doses, in another experiment using 11 other subjects. As in the preceding experiment, negative (placebo) and positive (morphine) control tests were made at weekly intervals in the same subjects.

The comparative effectiveness of the various agents in suppressing abstinence was evaluated by the paired *t*-test (3), using TAS values (total area scores) under the time-action curve for the 11 observations.

Results. — Carisoprodol partially but significantly ($P < 0.05$) suppressed symptoms of abstinence (figure 1), as tabulated by the hourly point score of Himmelsbach (8). Abstinence was

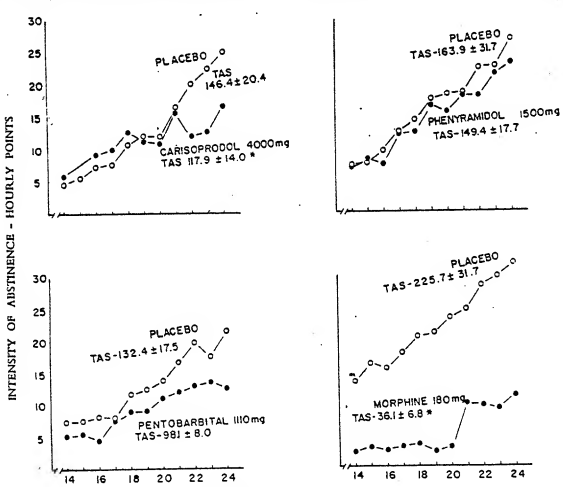

Figure 1. *Suppression of abstinence.* 24-hour substitution for morphine of carisoprodol, phenyramidol, pentobarbital, placebo, and morphine (positive control) continued in the customary dosage. Comparisons within individual graphs are cross-over, average comparisons in the same 9 subjects, except in the case of pentobarbital, when 11 subjects were used. TAS numbers refer to the mean total areas under the time-action curves ± standard error of the mean. Significant differences ($P < 0.05$) as compared to a placebo are shown by an asterisk. The total dosage of each drug substituted to suppress symptoms of abstinence from morphine is shown in milligrammes.

also suppressed partially by pentobarbital (figure 1), but not to a statistically significant degree ($P < .1$ and $> .05$). The 3 patients receiving the 4,800-mg substitution dose of carisoprodol were quite sedated and somewhat difficult to arouse, but showed only a slight degree of dysarthria and ataxia. All patients who received pentobarbital were sedated and showed a slight to moderate degree of ataxia and dysarthria; certain subjects were confused.

3. *Direct Addiction to Carisoprodol*

Methods. — Five non-tolerant subjects were used in a "single-blind" test — i.e., patients but not observers were unaware of the nature and schedule of medication. Starch placebos and carisoprodol powder were prepared in identically appearing capsules, and all medication was divided equally among four doses daily. All patients initially received placebo capsules for 12 days, 4 received carisoprodol for 18 days and one for 54 days. Carisoprodol was withdrawn abruptly and replaced by identically appearing capsules. The initial daily dose of carisoprodol was 1,200 mg; this was increased at a rate of 200 mg daily for 16 days to a daily dose of 4,200 mg, and then by 300 mg on the 17th and 18th days, attaining a daily dose of 4,800 mg. The patient receiving carisoprodol for 54 days received 4,800 mg daily from the 18th to the 54th day.

Observations were made three times daily throughout the experiment, and the degree of abstinence was calculated by the daily point scores of Kolb & Himmelsbach (10). In one patient, evidence of physical dependence was also evaluated (5) by administering 2 mg of nalorphine subcutaneously on the 44th day, and 5 mg on the 48th day of carisoprodol administration. Throughout the test, patients and aides independently completed a chronic dosage opiate questionnaire (7) at 7 p.m. daily. Clinical toxicity was evaluated by observations and by laboratory tests made prior to drug administration and repeated at bi-weekly intervals, when carisoprodol was administered, as follows: routine analyses of urine, red and white blood cell counts, hemoglobin content, hematocrit and liver function tests (thymol turbidity cephalin flocculation and evidence of bilirubin in the urine). An electrocardiogram was made on each patient while receiving placebos, and again after a high dosage of carisoprodol had been reached — i.e., 4,200 or 4,800 mg daily.

EEGs were obtained using an eight-channel resistance capacitance coupled Grass apparatus. Using needle electrodes, one bi-polar and three mono-polar tracings (linked and grounded) were obtained from frontal, temporal, parietal and occipital areas (4) prior to administering drugs to the 5 patients used in this direct addiction test. In 3 of these, the subsequent effect of a single 300-mg dose of carisoprodol was ascertained about one hour after carisoprodol was administered orally. In a similar manner, the effects of a single dose of 1,000 mg were determined in one patient, and those of 2,000 mg in another patient. During the direct addiction test, EEGs were taken on all 5 patients one hour after the 10 a.m. medication, when a daily dosage of 4,200 or 4,800 mg had been attained. The patient receiving carisoprodol for 54 days had an additional EEG after 45 days on the drug. During withdrawal, each of the 5 patients that had taken carisoprodol for 18 days had an EEG 18 and 36 hours after the last dose, and the patient that had carisoprodol for 54 days had one EEG 13 hours and another at 24 hours after the last dose.

Results. — During chronic administration of carisoprodol, except for changes in the EEG pattern, the outstanding feature was a complete absence of any significant subjective effects even when the dosage was increased to 4,800 mg daily. In other words, it was not possible to differentiate carisoprodol from a placebo (figure 1).

Following abrupt withdrawal of carisoprodol, the 4 patients that received it for 18 days showed no autonomic signs of abstinence, and did not realize that their medication had been changed. TAS scores (total scores under the time-action curve during the 10 days of withdrawal) averaged 77.3 during withdrawal as compared with an average TAS score of 41.0 observed during their last 10 days on carisoprodol. This increase in the abstinence scores during withdrawal is insignificant, particularly in view of the fact that the maximum daily score was only 10.3 points during withdrawal. The patient who received carisoprodol for 54 days showed no signs of abstinence when the drug was discontinued abruptly; the TAS score was 38 points, and the maximum daily score was only 7 points. This patient likewise stated that at no time did he feel the medication, and he was completely unaware of the fact that carisoprodol had been discontinued.

The EEG pattern after single doses of 300 mg showed questionable barbiturate-like effects as compared with the pre-drug EEG, but after single doses of 1,000 and 2,000 mg, and during chronic intoxication (4,200–4,800 mg daily), barbiturate-like effects were obtained. These changes consisted of rhythmic and non-rhythmic low- and medium-voltage fast activity (18–32 cps) seen more prominently in the frontal leads. In the 4 men who received carisoprodol for 18 days, the EEG patterns 17 and 36 hours after the last dose of the drug were normal. In the case of the patient who took carisoprodol for 54 days, the first EEG, taken 14 hours after the last dose of carisoprodol, showed a barbiturate-like effect, but the one taken 36 hours after the last dose was normal. None of these patients showed focal or generalized abnormalities of the paroxysmal type during withdrawal, such as those seen following withdrawal of barbiturates (9, 13, 4).

None of the clinical observations or laboratory tests showed significant deviations from pre-drug observations.

Chronic administration of carisoprodol on a progressive dosage schedule did not induce a characteristic barbiturate intoxication pattern (nystagmus, dysarthria, ataxia in gait and station, confusion, poor judgement and loss of emotional control), and when carisoprodol was abruptly withdrawn, no signs of barbiturate-like abstinence (anxiety, fine tremor, weakness, convulsions and delirium) were observed (9). However, it remains to be seen whether administering carisoprodol continuously in larger doses would induce a chronic state of intoxication and whether abrupt withdrawal under such circumstances would provoke a barbiturate or meprobamate type of abstinence. Such a possibility is suggested

by the fact that carisoprodol is a congener of meprobamate and exhibits many barbiturate-like pharmacological effects.

Part II. — Phenyramidol

1. *Effects of Single Doses*

Methods. — These were the same as those described for carisoprodol.

Results. — Seventeen tests in a dose range of 100-750 mg were conducted using non-tolerant subjects; 6 patients received the maximum dose of 750 mg. No effects were reported after any of these doses by any patient or observer, except sleepiness, which was noticed by one patient after a 750-mg dose. The pupils were not constricted. Neither the patients nor observers identified phenyramidol as an opiate; in fact, the most impressive finding was an absence of detectable objective or subjective pharmacological effects in these tests.

2. *24-hour Substitution of Phenyramidol for Morphine*

Methods. — These were the same as those outlined for carisoprodol.

Results. — Phenyramidol in a total dosage of 1,500 mg (divided into three equal doses) was substituted for 240 mg of morphine sulfate in 9 patients, and was compared with morphine (continued in the customary dosage) and with a placebo substituted in other tests using the same patients. As compared with a placebo, phenyramidol slightly depressed symptoms of abstinence from morphine, but the degree of suppression was statistically insignificant (figure 2).

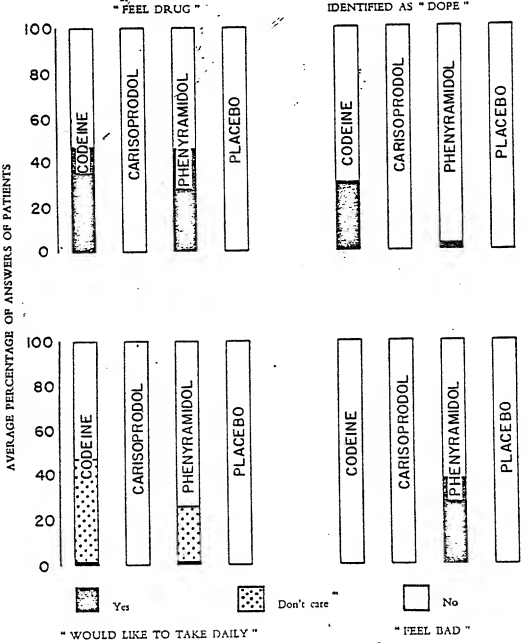

Figure 2. *Ratings of patients during direct addiction tests.* A comparison of the average percentage responses to the single dose questionnaire (patients' ratings) for codeine, carisoprodol, phenyramidol and a placebo for the parameters " feel drug ", " identification as ' dope ' ", " would like to take daily ", and " feel bad ". The comparison between codeine and a placebo was made with the same subjects in the same experiment, but other comparisons between drugs were made in analogous but different experiments using different subjects.

3. *Direct Addiction to Phenyramidol*

Methods. — Four non-tolerant subjects were used in a double-blind test — i.e., neither patients nor observers were aware of the nature and schedule of medication. Starch placebo and phenyramidol powder were prepared in identically appearing capsules, and all medication was divided into four equal doses daily. Initially all patients received placebo capsules for 7 to 10 days, then all were given phenyramidol for 18 days, after which the drug was abruptly withdrawn for two days. Medication was then resumed for an additional 42 days. The initial daily dose of phenyramidol was 600 mg, which was progressively increased until a daily dose of 4,500 mg was attained by the 18th day, and an attempt was made to stabilize patients on this dosage for the remainder of the experiment. After a total of 61 days of chronic drug administration, phenyramidol was withdrawn on a double-blind basis by replacing it with identically appearing placebo capsules.

Observations were the same as those made for evaluating carisoprodol, except EEGs and EKGs were not obtained.

Results. — One patient took phenyramidol for 16 days. The experiment was terminated on the 17th day, when a dosage of 4,200 mg had been attained, because he had diffuse urticaria. Prior to this, the only symptom noted by this patient was " sleepiness ". No symptoms or signs of abstinence developed after phenyramidol was discontinued, and the urticaria gradually subsided.

The other 3 patients attained a daily dose of 4,500 mg by the 18th day, and when medication was withdrawn abruptly for two days they showed no evidence of abstinence. Medication was resumed on the 21st day, but it was necessary to reduce the dosage of two patients to 3,300 mg daily because of such complaints as indigestion, sleepiness, dizziness and numbness of the skin (figure 2). One patient continued on 4,500 mg of phenyramidol daily, but he had a multiplicity of complaints; for example, he stated ". . . It made my face feel numb, I got a buzzing in both ears, and I had trouble hearing." He also described a sensation at times resembling effects of benzedrine or cocaine, which would last for only a few minutes. On the other hand, he had a relaxed feeling when he laid quietly in bed. Since these effects appeared contradictory to him, he inquired as to whether his medication had been changed from time to time. None of the patients liked the effects of phenyramidol, and the high incidence of " feel bad " reports as compared to the zero incidence of such reports during chronic intoxication with codeine is noteworthy (figure 2).

After 61 days of chronic intoxication, none of these patients realized that placebo capsules had been substituted. Abstinence scores were insignificant; in fact, they were smaller than comparably computed scores obtained while receiving phenyramidol.

Discussion

In the tests employed, neither carisoprodol nor phenyramidol showed any addictive properties of an opiate type. Although carisoprodol is pharmacologically similar in certain respects to barbiturates, it is not as rapidly acting as certain barbiturates. When the dosage of carisoprodol was rapidly increased from 1,200 to 4,800 mg daily within a period of 18 days, no evidence of intoxication was noted — suggesting that some tolerance developed to the sedative and hypnotic effects.

Summary and conclusions

The addictiveness of orally administered carisoprodol and phenyramidol has been studied in former opiate addicts. The procedures included effects of single doses, substitution tests to suppress abstinence from morphine, and direct addiction tests.

It is concluded that neither carisoprodol nor phenyramidol possesses addictive qualities of an opiate type.

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