each entry into a vial, the caps were rubbed with alcohol.

The results obtained with the phosphate buffer are presented in Table II. With sterile water, similar results were obtained but it was noticed after a few days that about half of the vials showed precipitation of the enol form. When precipitates were observed the vials were discarded. Since this would be unsatisfactory from a manufacturers as well as a clinical viewpoint, use of sterile water for reconstitution and multiwithdrawals is not recommended.

The data in Table II indicate that a vial of reconstituted warfarin sodium solution with disodium hydrogen phosphate buffer is quite stable over a reasonable period of time and can be used as a multidose vial.

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# Oral *versus* Subcutaneous Potency of Codeine, Morphine, Levorphan, and Anileridine as Measured by Rabbit Toothpulp Changes

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**The ratio of oral *vs.* subcutaneous potency of codeine, morphine, levorphan, and anileridine has been obtained using rabbit toothpulp threshold changes. Values for codeine, morphine, and levorphan were approximately equal. The value for anileridine was approximately one-half that of the other agents.**

MORPHINE is generally recognized to be inactive when administered orally (1). Likewise, oral codeine in doses up to 60 mg. is ineffective as an analgesic agent (2, 3). Levorphan (4) and anileridine (6), however, have been reported to have approximately equivalent analgesic potency by either oral or subcutaneous routes of administration. The differences in reported efficacy of these compounds by these routes prompted this study. The change in toothpulp thresholds in the rabbit was chosen to compare the oral *vs.* subcutaneous potency of codeine, morphine, levorphan, and anileridine.

## METHODS

Toothpulp threshold changes were measured as reported by Yim, *et al.* (5), using 0.7 to 1.5 Kg. rabbits. Fresh drug solutions were prepared daily in 0.9% saline and administered to the rabbit subcutaneously or orally by stomach tube.

The drugs utilized in this study were codeine phosphate, morphine sulfate, levorphan tartrate, and anileridine dihydrochloride. All doses were given in terms of $\mu$m./Kg. of the base.

The values for total area under the time-response curve were approximated as described by Winter and Flataker (7). These figures were obtained from the percentage changes of each individual rabbit. The peak percentage change during the first 90 minutes post drug was utilized in the analysis of peak responses.

A two by two parallel line bioassay was performed on all data except that of levorphan. A two by three parallel line bioassay was used in this instance. Both peak effect and total area under the curve responses were statistically analyzed by the method of Finney (8), using log response and log dose as effect and dose metameters, respectively.

## RESULTS

The results of the bioassay of oral *vs.* subcutaneous doses of codeine phosphate, morphine sulfate, levorphan tartrate, and anileridine dihydrochloride are presented in Figs. 1 and 2. Log dose was plotted against both the log of the total area under the response curve and the log of the peak response. The relative potencies with fiducial limits are summarized in Table I.

Table II illustrates the results of the analysis of variance for each of these groups.

## DISCUSSION

Our data demonstrate that codeine, levorphan, and morphine have subcutaneous-oral relative potency values of approximately equivalent magnitudes as measured by elevation of toothpulp thresholds in rabbits. This would be expected since they are close chemical congeners. Absolute potency, however, did vary from drug to drug. These data would thus be in agreement with the literature which

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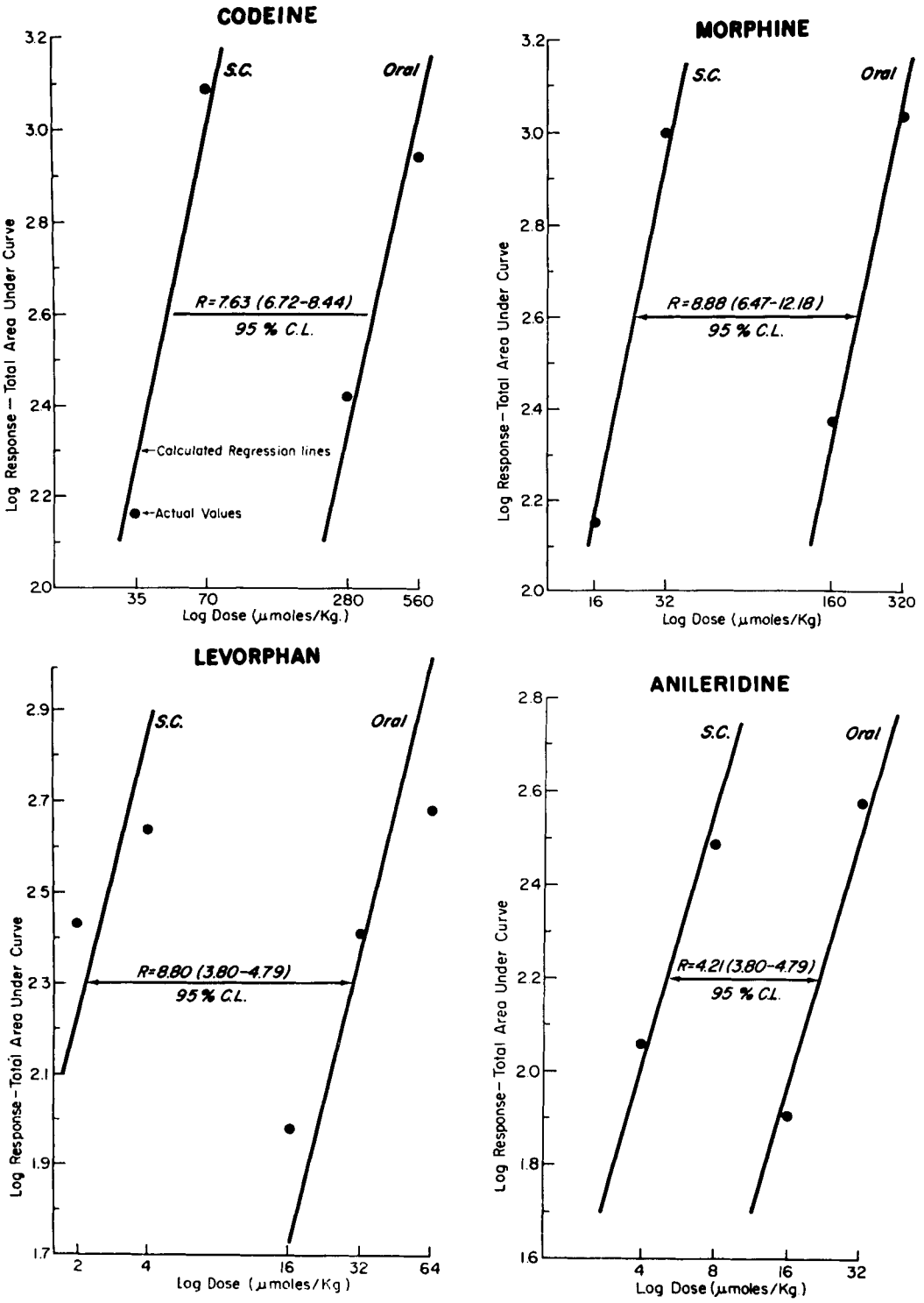


Fig. 1.—Results of bioassays of oral *vs.* subcutaneous codeine, morphine, levorphan, and anileridine. Response = total area under the curve.

reports codeine, morphine, and levorphan to be less active orally than parenterally in man. Anileridine has a relative potency value of approximately one-half that of the other compounds tested, although this figure does fall within the confidence limits for levorphan. This relative potency of anileridine is

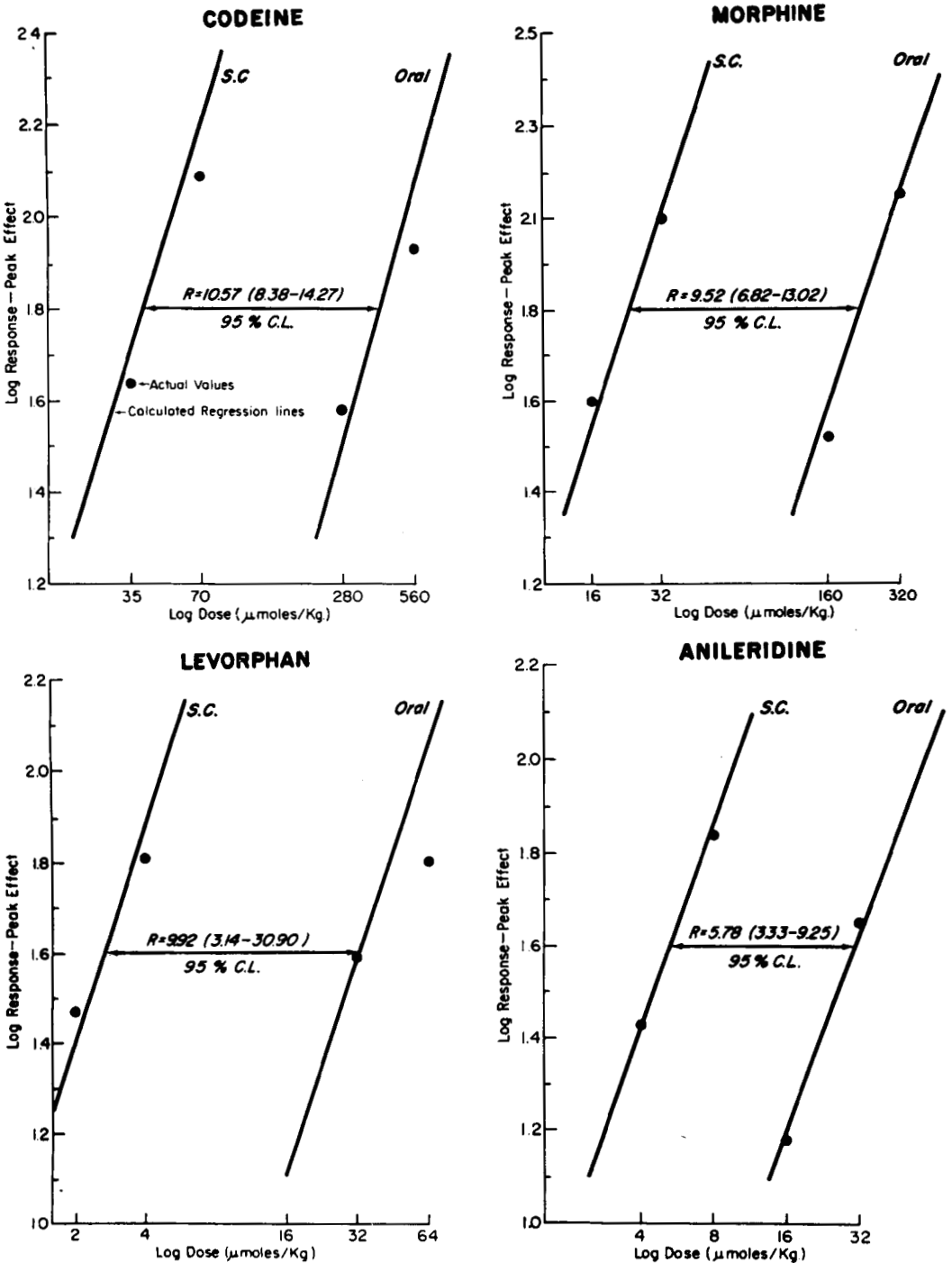


Fig. 2.—Results of bioassay of oral vs. subcutaneous codeine, morphine, levorphan, and anileridine. Response = peak effect.

similar to findings reported previously in rats (6), and would possibly be expected to differ from the values of the other agents since it is not closely related to them chemically.

Greater variations were found for peak response than for total area. Our results demonstrate that the relative potency values are greater when calculated from the peak effect figures than when calculated from the total area response data. This difference reflects the relatively lower peak effects following oral administration.

In the absence of clinical bioassay data it is

TABLE I.—RELATIVE POTENCY OF ORAL *VS.* SUBCUTANEOUS DRUG ADMINISTRATION

| Drug | Total Area Under the Curve | Peak Effects |
|---|---|---|
| Codeine | R = 7.63 (6.72- 8.44)[a] | R = 10.57 (8.38-14.27) |
| Morphine | R = 8.88 (6.47-12.18) | R = 9.52 (6.82-13.02) |
| Levorphan | R = 8.80 (2.58-28.47) | R = 9.92 (3.14-30.09) |
| Anileridine | R = 4.21 (3.80- 4.79) | R = 5.78 (3.33- 9.26) |

[a] Fiducial limits at the 95% confidence level.

TABLE II.—ANALYSIS OF VARIANCE OF BIOASSAY RESULTS PRESENTED IN FIGS. 1 AND 2.

| Total Area Under the Curve | | | | Peak Effects | | | |
|---|---|---|---|---|---|---|---|
| Source of Variation | d.f. | Mean Squares | F Ratio | Source of Variation | d.f. | Mean Squares | F Ratio |
| | | | Oral *vs.* s.c. Codeine | | | | |
| Preparations | 1 | 0.02 | 0.07 | Preparations | 1 | 0.42 | 6.63 |
| Regression | 1 | 5.28 | 19.48 | Regression | 1 | 2.47 | 37.42 |
| Parallelism | 1 | 0.42 | 1.55 | Parallelism | 1 | 0.21 | 3.18 |
| Between doses | 3 | 1.91 | | Between Doses | 3 | 1.03 | |
| Error | 36 | 0.27 | | Error | 36 | 0.07 | |
| Total | 39 | | | Total | 39 | | |
| | | | Oral *vs.* s.c. Morphine | | | | |
| Preparations | 1 | 0.16 | 0.40 | Preparations | 1 | 0.01 | 0.07 |
| Regression | 1 | 5.70 | 14.25 | Regression | 1 | 3.16 | 23.37 |
| Parallelism | 1 | 0.08 | 0.20 | Parallelism | 1 | 0.04 | 0.30 |
| Between doses | 3 | 1.98 | | Between Doses | 3 | 1.07 | |
| Error | 36 | 0.40 | | Error | 36 | 0.14 | |
| Total | 39 | | | Total | 39 | | |
| | | | Oral *vs.* s.c. Levorphan | | | | |
| Preparations | 1 | 0.39 | 1.22 | Preparations | 1 | 0.04 | 0.25 |
| Regression | 1 | 2.60 | 8.13 | Regression | 1 | 1.43 | 8.77 |
| Parallelism | 1 | 0.07 | 0.22 | Parallelism | 1 | 0.09 | 0.55 |
| Between doses | 4 | 1.82 | | Between Doses | 4 | 0.76 | |
| Error | 45 | 0.32 | | Error | 45 | 0.16 | |
| Total | 49 | | | Total | 49 | | |
| | | | Oral *vs.* s.c. Anileridine | | | | |
| Preparations | 1 | 0.01 | 0.04 | Preparations | 1 | 0.43 | 12.01 |
| Regression | 1 | 3.03 | 11.65 | Regression | 1 | 1.90 | 53.07 |
| Parallelism | 1 | 0.16 | 0.62 | Parallelism | 1 | 0.01 | 0.63 |
| Between doses | 3 | 1.06 | | Between Doses | 3 | 0.78 | |
| Error | 36 | 0.26 | | Error | 36 | 0.36 | |
| Total | 39 | | | Total | 39 | | |

difficult to assess the predictive value of this procedure. It is to be hoped that the pertinent human data will be available in the near future.

## SUMMARY

Changes in toothpulp threshold in rabbits have been measured following oral and subcutaneous codeine, morphine, levorphan, and anileridine. Codeine, morphine, and levorphan had approximately equal relative potency values. The relative potency value for anileridine, a structurally dissimilar compound, was approximately one-half that of the other agents. These data would thus agree with clinical reports that codeine, morphine, and levorphan are less active orally than when given parenterally. Relative potency values were greater when calculated from peak effect data than when calculated from the total area under the curves.

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