Clonixin: A Clinical Evaluation of a New Oral Analgesic

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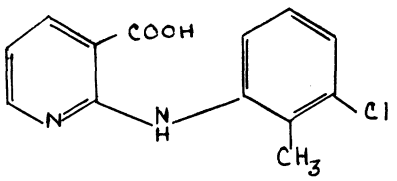
For the past several years, a large number of oral analgesic agents have been studied, but none of these has met the criteria for the ideal analgesic agent. This report will present our studies with a compound showing considerable promise.

Clonixin (CBA 93626) is a nonsteroidal, antiinflammatory analgesic. It is an anilino-nicotinic acid derivative. Its chemical formula is 2-(2′-methyl-3′-chloro)-anilino-nicotinic acid. It is a colorless to cream-colored solid with a molecular weight of 262.7. The compound has a very characteristic, extremely bitter, taste.



clonixin

Following an open, dose ranging, pilot study on 14 patients, which suggested effectiveness in pain relief and an absence of side effects, two studies were carried out at the University of Michigan utilizing clonixin. These were a comparison of clonixin given orally and morphine parenterally in postoperative orthopedic surgical patients and a comparison of clonixin and Darvon Compound* in postpartum patients. The last study was done at the Wayne County General Hospital.

Material and Methods

Patients selected for these studies were from the surgical wards of the University of Michigan Medical Center and from the obstetrical service of Wayne County General Hospital. Informed consent was obtained in all cases. Orders were written in such a fashion that the analgesic study nurse or technician was summoned each time the patient requested pain medication. Initially, patients were asked to categorize their pain as severe, moderate, or mild. Following this evaluation, they were given the first dose. At intervals of 30, 60, 120, 180, and 240 minutes, the patients were again seen and asked to categorize their pain. The patients were followed for a full 240 minutes after drug administration, unless additional medication was required for pain relief. If a patient required additional analgesic medication after 120 minutes the next dose in the series was administered.

In the evaluation of data, a value of plus 1 was assigned for each degree of decrease in pain. If pain became more severe, a value of minus 1 was assigned

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* Lilly trade name for mixture containing propoxyphene hydrochloride, aspirin, phenacetin, and caffeine.

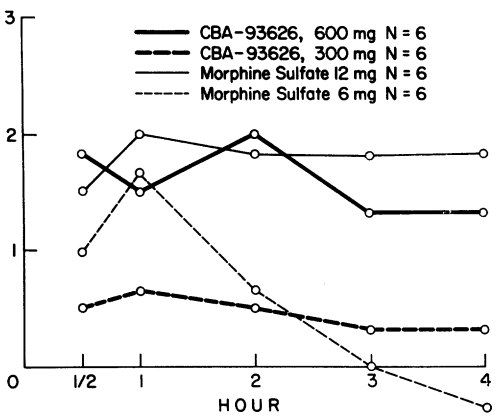

Fig. 1. Mean pain relief scores postoperative study (first dose only).

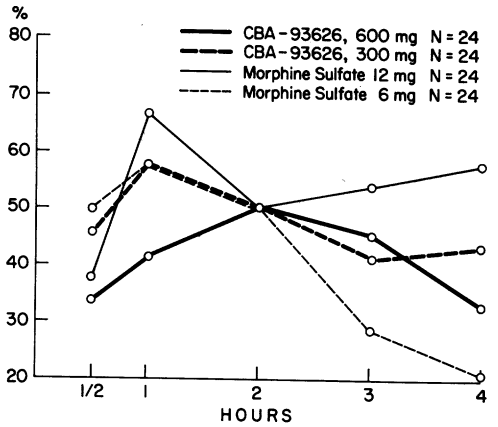

Fig. 2. Complete pain relief scores (all doses) postoperative study.

TABLE I

Postoperative Study Mean Pain Relief Scores (First Dose Only)

	½ hr	1 hr	2 hr	3 hr	4 hr
CBA 93626 600 mg (N=6)	1.83	1.50	2.00	1.33	1.33
CBA 93626 300 mg (N=6)	0.50	0.67	0.50	0.33	0.33
Morphine sulfate 12 mg (N=6)	1.50	2.00	1.83	1.83	1.83
Morphine sulfate 6 mg (N=6)	1.00	1.67	0.67	0.00	−0.33

TABLE II

Postoperative Study Complete Pain Relief Percentages (All Doses)

	½ hr	1 hr	2 hr	3 hr	4 hr
CBA 93626 600 mg (N=24)	30.4	41.6	50.0	45.8	33.3
CBA 93626 300 mg (N=24)	45.8	58.3	50.0	41.6	43.5
Morphine sulfate 12 mg (N=24)	37.5	67.0	50.0	54.2	58.3
Morphine sulfate 6 mg (N=24)	50.0	58.3	50.0	29.2	21.0

for each degree of increase in pain. If medication had to be repeated in less than 4 hours, a value of zero was assigned to all remaining interview points. If the patient was asleep at any interview point, he was not awakened and his pain was recorded as none. Side effects were recorded only when obvious or reported by the patient.

Comparison of Clonixin and Morphine

In this evaluation a comparison was made between clonixin 300 and 600 mg (orally) and morphine sulfate 6 and 12 mg (intramuscularly). The experimental design was a double blind crossover, with each patient receiving both an intramuscular injection (active and placebo) and an oral medication (active and

TABLE III

Postoperative Study Satisfactory Pain Relief (All Doses)

	Dosage (mg)	No. pts.	% of total interviews
CBA 93626	600	24	41.7
CBA 93626	300	24	30.4
Morphine sulfate	12	24	50.0
Morphine sulfate	6	24	25.0

TABLE IV

Postoperative Study Side Effects

	CBA 600 mg	CBA 300 mg	M.S. 12 mg	M.S. 6 mg
Dizziness	2	0	0	0
Drowsiness	7	4	8	5
Nausea	2	0	2	0
Vomiting	1	2	2	1
Diaphoresis	1	1	1	1
Epigastric distress	1	0	1	0
Headache	1	0	0	0
Pruritis	0	1	1	0
Insomnia	0	1	0	0
Chills	0	0	1	0
Irritability	0	0	0	1
Dry mouth	0	0	0	1
Auditory disturbance	0	0	0	1
Euphoria	1	0	0	0

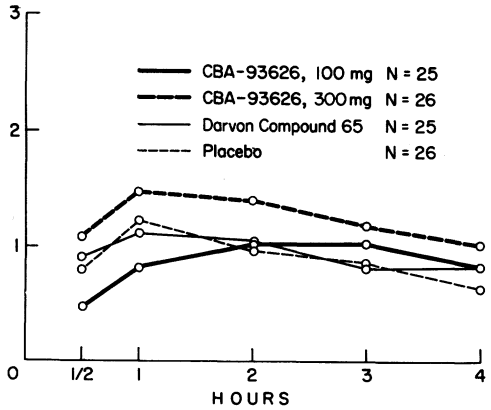

Fig. 3. Pain relief scores postpartum study (Group I).

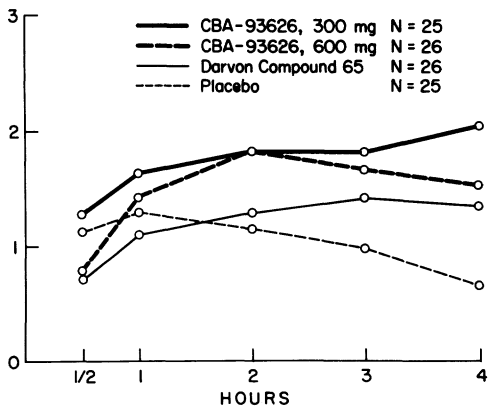

Fig. 4. Pain relief scores postpartum study (Group II).

placebo) at each treatment point. Twenty-four patients were included in the study, 16 males and eight females. Patients ranged in age from 21 to 68 years with a mean age of 38. Weight ranged from 126 to 210 pounds, with a mean weight of 173.8 pounds.

Postpartum Studies

In this evaluation we sought to test the compound in a different pain model. Clonixin in doses of 100, 300 and 600 mg, Darvon Compound 65 mg, and placebo were compared in the control of postpartum pain. The experimental design of this portion of the study was a double-blind, single-dose method; all treatments were randomized; a second dose of Darvon Compound 65 mg was administered 2 hours after the initial dose if the patient requested remedication.

Two hundred and four postpartum patients were included in this study. Patients ranged in age from 21 to 30 years, with a mean age of 24. Weight distribution was from 89 to 240 pounds, with a mean weight of 131 pounds.

In the first 102 patients, clonixin 100 and 300 mg were compared with Darvon Compound 65 mg and placebo. In the second 102 patients, clonixin 300 and 600 mg were compared with Darvon Compound 65 mg and placebo.

Results

Comparison of Clonixin and Morphine

Mean Pain Relief Scores (Figure 1, Table I). The data presented here represent the mean pain relief scores at each interview point. Only first doses are considered, to exclude any possible order effect. At the 2-hour point there is a clear separation of higher from lower doses, and clonixin 600 mg produces pain relief comparable to that with morphine sulfate 12 mg (significant at the 0.05 level).

Complete Pain Relief (Figure 2, Table II). These data represent the numbers of patients reporting no pain at given interview points, expressed as a percentage of the total interviews. No separation is possible at 2 hours, but at 3 hours clonixin appears to produce pain relief midway between the two doses of morphine.

TABLE V

Postpartum Study Pain Relief Scores (Group I)

	½ hr	1 hr	2 hr	3 hr	4 hr
CBA 93626 100 mg (N=25)	0.48	0.80	1.00	1.00	0.82
CBA 93626 300 mg (N=26)	1.08	1.46	1.38	1.27	1.00
Darvon Compound 65 mg (N=25)	0.88	1.12	1.00	0.80	0.80
Placebo (N=26)	0.77	1.19	0.96	0.81	0.63

TABLE VI

Postpartum Study Pain Relief Scores (Group II)

	½ hr	1 hr	2 hr	3 hr	4 hr
CBA 93626 300 mg (N=25)	1.28	1.64	1.84	1.80	2.04
CBA 93626 600 mg (N=26)	0.77	1.42	1.77	1.65	1.50
Darvon Compound 65 mg (N=26)	0.73	1.08	1.28	1.42	1.33
Placebo (N=25)	1.12	1.28	1.13	0.96	0.65

Satisfactory Pain Relief (Table III). To be classified as "satisfactory," relief within the first hour from severe or moderate initial pain must be valued as at least plus 2 and from mild initial pain as plus 1. Relief must remain at that level for 2 additional hours. Again, clonixin 600 mg and morphine sulfate 12 mg seem comparable.

Side Effects (Table IV). There were no significant side effects.

Postpartum Studies

Pain Relief Scores (Figures 3 and 4, Tables V and VI). In the first 102 patients, Darvon Compound 65 mg, clonixin 100 mg, and a placebo were grouped very closely at all time periods. Clonixin 300 mg does maintain slightly higher pain relief scores over the four periods, but this is not statistically significant. Pain relief scores in the second group of 102 patients shows a little wider spread. This spread is most pronounced at the 2-hour point, at least when the investigational compound doses are compared with Darvon Compound or the placebo.

Complete Pain Relief (Figures 5 and 6, Tables VII and VIII). In the first 102 patients, little separation between any of the compounds tested is shown, whereas in the second group of 102 patients, wide separation is apparent at the 2-hour point, some 60 per cent of patients expressing complete pain relief with Darvon Compound 65 mg at 2 hours, as compared with 85 per cent of the patients receiving the comparable doses of clonixin.

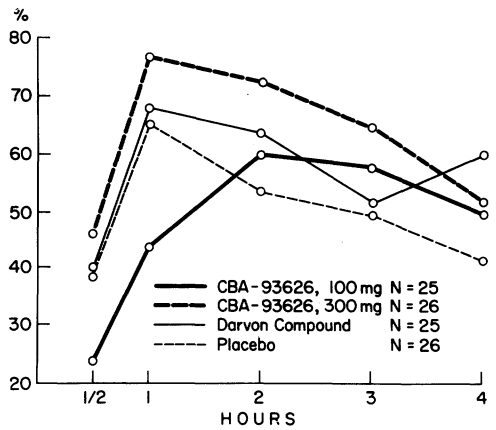

Fig. 5. Complete pain relief scores postpartum study (Group I).

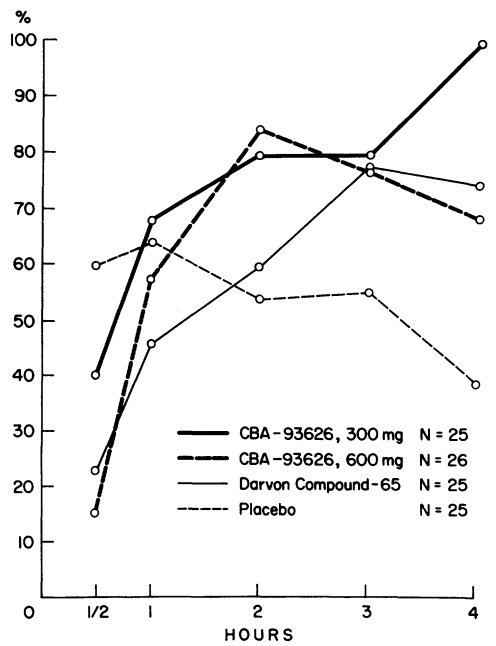

Fig. 6. Complete pain relief scores postpartum study (Group II).

TABLE VII

Postpartum Study Complete Pain Relief Percentages (Group I)

	½ hr	1 hr	2 hr	3 hr	4 hr
CBA 93626 100 mg (N=25)	24.0	44.0	60.0	58.3	50.0
CBA 93626 300 mg (N=26)	46.2	76.9	73.1	65.4	52.0
Darvon Compound 65 mg (N=25)	40.0	68.0	64.0	52.0	60.0
Placebo (N=26)	38.5	65.4	53.8	50.0	41.7

TABLE VIII

Postpartum Study Complete Pain Relief Percentages (Group II)

	½ hr	1 hr	2 hr	3 hr	4 hr
CBA 93626 300 mg (N=25)	40.0	68.0	80.0	80.0	100.0
CBA 93626 600 mg (N=26)	15.4	57.7	84.6	77.0	69.2
Darvon Compound 65 mg (N=26)	23.1	46.2	60.0	79.2	75.0
Placebo (N=25)	60.0	64.0	54.2	56.5	39.1

TABLE IX

Postpartum Study Satisfactory Pain Relief Percentages (Group I)

	Dosage (mg)	No. pts.	% of total interviews
CBA 93626	100	25	32.0
CBA 93626	300	26	50.0
Darvon Compound	65	25	48.0
Placebo	—	26	53.8

TABLE X

Postpartum Study Satisfactory Pain Relief Percentages (Group II)

	Dosage (mg)	No. pts.	% of total interviews
CBA 93626	300	25	68.0
CBA 93626	600	26	65.4
Darvon Compound	65	26	42.3
Placebo	—	25	40.0

Satisfactory Pain Relief (Tables IX and X). The ability of the higher doses of clonixin to achieve the criteria for satisfactory pain relief is striking.

Discussion

Based upon our early experience with the drug in the pilot study, we felt that clonixin did have clinically detectable analgesic activity.

The study comparing clonixin with morphine seemed to substantiate our early impressions concerning the analgesic potency of clonixin and define even more the relative potency of the drug. It appeared clinically that clonixin in doses of 600 mg orally would be approximately equal to 8 to 10 mg of morphine sulfate parenterally. The absence of significant side effects was encouraging.

The postpartum phase of this study served to clarify the picture further. In the first group of 102 patients, it was apparent that clonixin in doses of 100 and 300 mg was an inadequate analgesic. However, in the second 102 patients, using a higher dose, very satisfactory pain relief scores were obtained, especially at the 2-hour point, with 600 mg of clonixin.

TABLE XI

Postpartum Study Side Effects

	CBA 100 mg	CBA 300 mg	CBA 600 mg	Darvon Cpd. 65 mg	Placebo
Nausea	0	2	0	2	1
Vomiting	0	0	0	0	1
Drowsiness	0	2	2	9	3
Visual disturbance	0	0	0	1	0
Headache	1	1	0	1	0
Dry nose & mouth	0	1	0	0	0
Hot flashes	1	0	0	0	0
Diaphoresis	1	0	0	0	0
Proteinurea*	0	4	3	1	3

* Of the 203 patients in whom the study was completed, 67 of the second group obtained urine specimens and were tested for proteinurea.

Summary

Clonixin (CBA 93626) is a nicotinic acid derivative which has antiinflammatory and analgesic properties. This study presents evidence of its effectiveness in two controlled clinical evaluations. Comparisons were made in postsurgical and postpartum patients using a variety of standard analgesics for reference. Clonixin 600 mg orally is clinically comparable to morphine sulfate 10 mg parenterally.

Acknowledgment

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