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Absorption rates of alphaprodine from the buccal and intravenous routes

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Abstract

Alphaprodine is a rapidly acting synthetic narcotic. The effectiveness and rate of absorption when this drug is administered buccally is not known. The purpose of this study is to investigate absorption rates of alphaprodine administered buccally, (submucosally) and intravenously. Eight healthy male volunteers ranging in age from 19 to 41 years were included. Each subject received 0.4 mg/kg of body weight of alphaprodine buccally and intravenously. Blood samples of 2-3 ml were collected at 1, 2, 5, 10, 15, 20, 30, and 40 minutes. All blood samples were collected in heparinized test tubes and stored in ice for gas-liquid chromatographic analysis. Data were subjected to a 2 x 8 analysis of variance for repeated measures employing the BMDP2V statistical program, and the Scheffe test for multiple comparisons. Buccal administration exhibited a low initial concentration increasing constantly and peaking at the 10 minute level, followed by a steady decline which was higher but parallel with intravenous concentration decline. The differences between the buccal and the intravenous route were only significant at the one and two minute levels, when the intravenous route blood concentrations were higher. After the two minute level, the differences were not statistically significant. It is concluded that the administration of alphaprodine via buccal route is a highly efficient alternative to the intravenous route. Subjective evaluation of the sample indicated a longer recovery period following buccal administration. Also, pain following buccal administration was often pronounced.

Alphaprodine is a fast acting synthetic narcotic. The pharmacological properties of this drug closely resemble those of meperidine and morphine.[1] Alphaprodine is considered 2.5 to 3 times as potent as meperidine, with shorter duration.[2]

This drug, because of its potency and ideal length of effectiveness, has gained tremendous popularity.[3] The rate of absorption when this drug is administered intravenously is well documented, however such documentation is totally lacking when this drug is administered buccally (submucosally).

The objective of this study was to investigate absorption rates of alphaprodine when administered buccally (submucosally), and to compare it to absorption rates of the drug when administered intravenously. Also, certain subjective responses would be evaluated.

Literature Review

Alphaprodine is dl-1, 3-dimethyl-4-phenyl-4-piperidinol proprionate hydrochloride. Its chemical structure is very similar to meperidine.[4] It was first introduced in 1947 by Ziering and Lee.[5] Its first clinical application was in obstetric medicine where it was found effective in reducing or eliminating labor pain.[6,7] The drug thereafter began to gain popularity in anesthesia and other medical disciplines.[8]

It was used either by itself or in combination with other drugs such as narcotic antagonists, promethazine, or other tranquilizers.[9,10] The manufacturer suggested an intravenous or subcutaneous route of administration.[4] The recommended adult dose was 0.4 to 0.6 mg per kg of body weight, if administered intravenously; and 0.4 to 1.2 mg per kg when administered subcutaneously.[4] Such dosage recommendation was applicable to single drug administration: therefore it should be reduced if the drug is used with promethazine or other drugs.[11]

Several complications have been reported. Respiratory depression, as with other narcotic analgesics, has been the major and most frequently encountered adverse reaction produced by alphaprodine. Several cases of major complications have been reported, usually when the drug was used in combination with other drugs.[12,13] Other complica-

tions or side effects include dizziness, sweating, and urticaria.[14]

Alphaprodine was introduced to dentistry and rapidly gained popularity. The preferred route of administration by most dentists was the buccal route. Dose calculation for buccal administration was empirical and soley based on the operator's judgement rather than any scientific evidence — or even manufacturer's recommendations. Roche Laboratories discontinued the sale of alphaprodine temporarily because of usage in a manner contrary to the package insert recommendations.[15]

Methods and Materials

Eight healthy male volunteers ranging in age from 19 to 41 years were included. All subjects were screened carefully to exclude any with history of allergic reaction to narcotic analgesics or history of previous exposure to narcotics. Volunteers were particularly screened for any renal or hepatic diseases. None of the volunteers were taking any medications. Every patient received a complete blood count prior to the initiation of the study. All volunteers were instructed to fast for a minimum of six hours prior to their appointments. A minimum of two weeks were planned between appointments. The sequence of administration was alternated in order to allow each route an equal chance of being first. Pre-administration routine included complete blood count, blood pressure, pulse, and respiration.

For each administration, a teflon catheter was inserted into an accessible vein in the right antecubital fossa. A baseline blood sample of 2-3 ml was collected. Subjects were then administered alphaprodine over a 60 second period. Buccal submucosal injections were administered into the mucobuccal fold of the maxillary left first permanent molar following the application of topical anesthetic. Negative aspiration was achieved in every case. All drug administrations were performed by the same operator. Each subject received 0.4 mg/kg of body weight of alphaprodine. Blood samples of 2-3 ml were collected at 1, 2, 5, 10, 15, 20, 30 and 40 minutes. Each subject was in a supine position with blood pressure, pulse, and respiration monitored every five minutes. Subjective evaluation of lethargy, dryness of mouth, euphoria, light headedness, nausea, pain in the injection site, and time lapse perception was attempted and rated by each volunteer on a six point scale (0-5). All blood samples were collected in heparinized test tubes and stored in ice for gas-liquid chromatographic analysis according to the method of Fung and coworkers.[16]

Results

The mean plasma levels for each route of administration were tabulated and plotted graphically (Figure 1; Table 1). Following intravenous administration, the maximum mean plasma concentration was 0.275 μg/ml. This was achieved at the one minute level, and was followed by a steady decline to a low of 0.095 μg/ml at the 40 minute level.

Following buccal administration, the initial plasma level was relatively low at 0.023 μg/ml but demonstrated a steady increase and peaked with 0.239 μg/ml at the 10 minute level. This peak was followed by a steady decline to 0.126 μg/ml concentration at the 40 minute level. From the 10 minute level to the 40 minute levels, the buccal route concentrations were consistently higher than the intravenous route.

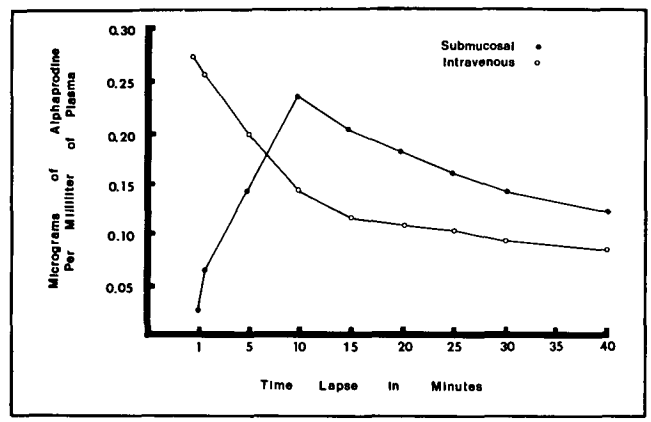

Figure 1. Mean plasma levels for each route of administration.

Statistical evaluation of the mean values obtained from the two routes at various time intervals did not indicate the presence of statistically significant differences for either the main effects or the route of administration ($F=0.50$; $df=1,7$; $P=0.50$); or time interval ($F=1.66$; $df=7,3=49$; $P=0.001$). Using the Sheffe test for multiple comparisons, significant differences at the 0.05 level existed only at the one and two minute levels where the intravenous concentrations were higher. After the two minute interval, the differences were not statistically significant. Subjective evaluation of the sample indicated a longer recovery period following buccal administration.

Recovery period following intravenous administration ranged from one hour and thirty minutes to three

Table 1. Mean values of alphaprodine in plasma (in micrograms).

Time	1 min.	2	5	10	15	20	25	30	40
IV Route	.275	.260	.202	.148	.129	.117	.110	.103	0.095
Buccal Route	.023	.067	.146	.239	.201	.178	.164	.151	.126

hours. Recovery period following buccal administration ranged from two hours and thirty minutes to seven hours. The mean recovery period was 1.68 hours for the intravenous administration, compared to 3.5 hours for the buccal administration. Pain following buccal administration was more pronounced than pain following intravenous administration.

Discussion

Previously, the buccal (submucosal) administration of alphaprodine was advocated empirically. There were no scientific data regarding dose calculation, relative effectiveness, length of recovery period, and its interaction with other drugs.

Serious complications have been reported which can be traced primarily to inappropriate dose calculations.[12,13] It is quite obvious that many practitioners calculated their doses for buccal administration, on the basis of the manufacturer's subcutaneous route doses, or on erroneous textbook information, thus overdosing practically every patient they treated.

This study indicates the presence of a close relationship between the buccal and the intravenous routes. More striking, however, is the indication that the bucccal route may be even more efficient, at later time intervals, although the difference was not statistically different. This higher concentration as well as the prolonged recovery periods following buccal administrations indicate the possible presence of a secondary phase due to this drug's affinity to fatty tissues. These tissues in turn release the drug at a slower rate. Anatomically, the site of the buccal injections in this study, yields some support to this hypothesis.

Due to the efficiency of the buccal administration of this drug, it is obviously important to monitor patients who receive it very closely, thus reducing or minimizing its potential side effects. If this approach is combined with appropriate adjustments of recommended doses for buccal administration, a much safer yet very effective and valuable drug can be restored to the market place.

Conclusion

1. Buccal administration of alphaprodine is a highly efficient alternative to the intravenous administration.
2. Dosage for buccal administration should be calculated on the basis of the intravenous route dosages as recommended by the manufacturer.
3. Prolonged recovery periods following the buccal administration may necessitate longer observation periods than previously suggested.
4. Buccal administration can be painful for a period lasting up to approximately five minutes.
5. Changes in vital signs, as monitored in this study, were variable but minimal and did not indicate any specific trends.

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