# The Empiric Use of Naloxone in Patients With Altered Mental Status: A Reappraisal

Jerome R Hoffman, MD, FACEP*†
David L Schriger, MD, MPH*†
John S Luo†
Los Angeles, California

From the Department of Medicine, UCLA School of Medicine;* and the UCLA Emergency Medicine Center,† Los Angeles, California.

Received for publication July 9, 1990. Revision received September 20, 1990. Accepted for publication October 29, 1990.

Presented in part at the Society for Academic Emergency Medicine Annual Meeting in San Diego, May 1989.

Address for reprints: Jerome R Hoffman, MD, FACEP, Department of Medicine, UCLA Emergency Medicine Center, 924 Westwood Boulevard, Suite 300, Los Angeles, California 90024.

Study objective: *To determine whether clinical criteria (respirations of 12 or less, miotic pupils, and circumstantial evidence of opiate abuse) could predict response to naloxone in patients with acute alteration of mental status (AMS) and to evaluate whether such criteria predict a final diagnosis of presence or absence of opiate overdose as accurately as response to naloxone.*

Cases and setting: *Seven hundred thirty patients with AMS who received naloxone for diagnostic or therapeutic purposes at the discretion of two large, urban, paramedic base teaching hospitals.*

Methods: *We reviewed paramedic run sheets and audiotapes on all 730 patients as well as available hospital records of all patients who demonstrated any response to naloxone to determine whether overdose was responsible for their clinical presentations. We also reviewed hospital records for a selected sample of naloxone nonresponders.*

Main results and conclusion: *Only 25 patients (3.4%) demonstrated a complete response to naloxone, whereas 32 (4.4%) manifested a partial or equivocal response. Nineteen of 25 complete responders (76%), two of 26 partial responders (8%) (with known final diagnosis), and four of 195 nonresponders (2%) (with known final diagnosis) were ultimately diagnosed as having overdosed. Respirations of 12 or less or the presence of any one of the three clinical findings as a group were each highly sensitive in predicting response to naloxone, and at least as sensitive as response to naloxone in predicting a diagnosis of opiate overdose. Selective administration of naloxone for AMS would have decreased the use of this drug by 75% to 90% while still administering it to virtually all naloxone responders who had a final diagnosis of opiate overdose. [Hoffman JR, Schriger DL, Luo JS: The empiric use of naloxone in patients with altered mental status: A reappraisal. Ann Emerg Med March 1991;20:246-252.]*

## INTRODUCTION

Since its introduction in 1967, naloxone has greatly improved the treatment of patients with opiate overdose. Enthusiasm regarding the benefits of this drug in certain patients has resulted in the broad recommendation that an initial dose of 0.8 to 2.0 mg naloxone be given to all patients with acute alteration in mental status (AMS).[1-3] Proponents of this strategy argue that naloxone is an accurate diagnostic tool for the confirmation or exclusion of opiate overdose and that it also provides therapeutic benefit to some narcotized patients. Because naloxone has been described as being free of substantial adverse effects, this strategy of empiric administration in all cases of acute AMS has become extremely popular, despite the fact that its usefulness has never been tested.

After many years of using this policy of empiric naloxone administration, we have begun to question its value, particularly regarding its diagnostic usefulness. In our experience, it has been always possible to predict on the basis of easily determined clinical findings which patients will respond to the drug. Furthermore, diagnostic information gained in some patients with a clear response to naloxone is often offset by diagnostic confusion created in a substantial number of others with an equivocal response as well as in patients with false-negative (mixed drug overdoses) or false-positive (fortuitous awakening around the time naloxone is given) re-

actions.

In addition, there is a growing body of evidence that while naloxone is very safe in the emergency department setting, it is not completely without toxicity that can be quite severe.[4-6] Furthermore, even the therapeutic advantage of early administration of naloxone is unclear for most patients: In the absence of respiratory depression, patients with opiate overdose are usually in no acute danger. In addition, some patients experience sufficient arousal to allow them to be combative, refuse medical care, and risk the significant complications that can occur because the half-life of naloxone is shorter than that of most street narcotics. Finally, although the availability of generic naloxone since 1986 has substantially reduced the cost of the drug, its empiric administration to the many thousands of AMS cases nationally each year still results in considerable aggregate costs, which could be dramatically decreased by limiting use of the drug to selected patients.

It was our intent in this study to focus exclusively on the possibility that the diagnostic value of naloxone is limited in patients with nonspecific AMS. To this end, our primary hypothesis was that response to naloxone in such patients is almost always predictable on the basis of easily determined clinical characteristics.

Our secondary hypothesis was that these same clinical characteristics perform at least as well as response to naloxone in identifying patients for whom a clinical diagnosis of opiate overdose is ultimately made. If true, this would allow us to restrict the prehospital administration of naloxone to only those AMS patients for whom it might be expected to have therapeutic benefit, thereby drastically decreasing the number of patients who receive this drug without in any significant way diminishing the quality of care delivered to patients with opiate intoxication. Such a policy should also minimize the diagnostic confusion currently created by partial or questionable responses to naloxone and improve the prehospital care of AMS patients who do not suffer from opiate intoxication.

## MATERIALS AND METHODS

The study population comprised all patients who received naloxone as part of the prehospital treatment prescribed by two busy Los Angeles paramedic radio base stations. UCLA base, situated in the UCLA Emergency Medicine Center, provides medical control for six paramedic units in a predominantly middle-class area of Los Angeles. Paramedic calls handled by this base during a 12-month period beginning in December 1986 were eligible for inclusion in this study.

Harbor base, located at Harbor-UCLA Medical Center, a UCLA-affiliated county hospital, provides primary radio control for four paramedic units in an economically deprived area of Los Angeles County; calls handled by this base during the first six months of 1986 were included in the study. The catchment area of the units controlled by Harbor base has a prevalence of opiate abuse that is expected to be higher than that of the Los Angeles norm, whereas the UCLA-affiliated paramedic units are located in areas in which opiate abuse is thought to be less endemic.

The paramedic run sheets and tape-recorded paramedic-base hospital communications for all patients treated at each base station during the study period were reviewed. Patients were included in the study if they were given naloxone for AMS. Data collected included the patient's response to naloxone as well as three specific clinical findings; these findings were respirations, pupil size, and presence or absence of circumstantial evidence of opiate abuse. Respirations and pupil size were chosen because they are considered reliable signs of opiate intoxication, and Los Angeles paramedics record these parameters on essentially all patients they treat. Respirations were scored as depressed (12 or less) or normal (more than 12), and pupils were scored as pinpoint or normal.

A patient was scored as having circumstantial evidence of opiate abuse only if paramedics noted the presence of drug paraphernalia at the scene, needle track marks on the skin, or a history of IV drug use given by bystanders. Paramedics are trained to look for this circumstantial evidence and will generally document such findings when they are present; when the run sheet and tape recording failed to document the presence or absence of one or more of these circumstantial signs, the data sheet was scored as negative for this value. Response to naloxone was scored as complete, partial/equivocal, or absent on the basis of information provided to the base hospital by paramedics at the scene.

We attempted to obtain the hospital charts of all study patients treated by the UCLA base as well as all patients from Harbor base with either complete or equivocal responses. Because there is no formal link between the prehospital run sheet and the patient's hospital chart at Harbor-UCLA Medical Center, it would have been prohibitively difficult to identify and obtain hospital charts of all patients whose prehospital care was supervised by this facility; therefore, we intentionally limited our nonresponder sample to patients handled by the UCLA base. To ensure that this sample was representative of the total population of nonresponders, we compared prehospital clinical characteristics of UCLA nonresponders with a random sample of 100 nonresponders handled by Harbor base.

The hospital charts of all naloxone responders, partial responders, and the sample of nonresponders were reviewed by one of the physician authors to determine whether opiate overdose was included as a discharge diagnosis. The reviewing physician was unaware of the patient's response to naloxone when he made this decision. The presence or absence of opiate overdose was then added to the patient's data form.

We tested our primary hypothesis, that naloxone response can be predicted by clinical characteristics, by evaluating the concordance between the chosen clinical findings and the response to naloxone. We tested our secondary hypothesis, that clinical findings identify patients with opiate overdose, by comparing the performance of clinical predictors and naloxone response with regard to the ultimate clinical diagnosis.

We specifically chose final clinical diagnosis rather than laboratory proof of presence or absence of opiate use as the gold standard regarding our secondary hypothesis for several reasons. First, toxicologic analysis of opiates is notoriously poor, both because some important street narcotics like fentanyl are tested for in

**TABLE 1.** *Sensitivity and specificity of the clinical findings in predicting response to naloxone*

| | Response to Naloxone | | | | |
|---|---|---|---|---|---|
| | Complete Awakening | | Partial Response | No Response | |
| Clinical Parameter | N | Sensitivity (%)*† | (N) | N | Specificity (%)‡ |
| Respirations ≤ 12 | 20 | 80 | 1 | 18 | 95 |
| Pinpoint pupils | 22 | 88 | 5 | 33 | 90 |
| Circumstantial evidence | 15 | 60 | 6 | 21 | 94 |
| Any one of the above | 24 | 96 | 10 | 50 | 85 |
| Total patients | 25 | | 32 | 337 | |

*Sensitivity and specificity calculated with the partial responders deleted.
†Sensitivity = N/25.
‡Specificity = 337 − N/337.

**TABLE 2.** *Sensitivity and specificity of the clinical findings and of naloxone response in predicting a diagnosis of opiate overdose in 246 patients with known final diagnosis*

| Clinical Parameter | Sensitivity (%) (95% CI) | Specificity (%) (95% CI) |
|---|---|---|
| Respirations ≤ 12 | 79 (57 − 92%) | 94 (89 − 96%) |
| Pinpoint pupils | 75 (53 − 89%) | 85 (80 − 89%) |
| Circumstantial evidence | 67 (45 − 84%) | 95 (92 − 98%) |
| Any one of the above | 92 (72 − 99%) | 76 (70 − 81%) |
| **Naloxone Response** | | |
| Partial responders scored as responders | 88 (67 − 97%) | 86 (81 − 91%) |
| Partial responders scored as nonresponders | 79 (57 − 92%) | 97 (94 − 99%) |
| Partial responders omitted | 86 (64 − 96%) | 97 (93 − 99%) |

only a few very specialized laboratories and because even more standard agents such as heroin or methadone are routinely misidentified by most commercial laboratories.[7-9] Thus, the absence of opiates on laboratory analysis does not reliably exclude narcotism as a cause of AMS. Second, even if accurate toxicologic analysis could be performed routinely, the mere presence of opiates on qualitative screening in no way implies that this is the cause of AMS. Furthermore, laboratory results are not available for at least several hours, which would severely restrict any benefit of naloxone response as a screening test used to limit need for other diagnostic modalities (eg, computed tomography or lumbar puncture).

Most important, our study is primarily an attempt to determine whether naloxone provides a diagnostic benefit to clinicians; thus, regardless of what might have been found with routine and extensive laboratory testing for opiates, naloxone's use for the clinicians treating the patients in this series could not have been greater than the extent to which it in fact helped them reach or exclude the diagnosis of narcotism. Although response to naloxone undoubtedly influenced the ultimate clinical diagnosis in some or even many of the cases, this can only have biased our results *in favor of* naloxone's value (and thus against our hypothesis) because this could only increase the correspondence between response to naloxone and final diagnosis.

Sensitivity and specificity were calculated in the standard manner.[10] To maximize the likelihood of finding a diagnostic benefit of naloxone, we performed this calculation in three different ways based on each of three possible assumptions: 1) that partial responders should be considered as having a positive response to naloxone, which would maximize sensitivity at the expense of specificity; 2) that partial responders not be considered as having a positive response, because in our experience few of these patients ultimately prove to have opiate overdose; and 3) that a partial response is uninterpretable and thus such patients should be removed from consideration, which may maximize accuracy in patients with clear or absent response to naloxone at the expense of eliminating a potentially substantial portion of the original population.

Ninety-five percent confidence intervals (CIs) for all parameters were calculated using the exact method of Fleiss; statistical tests comparing differences between proportions were calculated in the usual manner.[11] The null hypothesis that the clinical findings and the response to naloxone were identical in predicting a final diagnosis of opiate intoxication was evaluated with McNemar's test.[12]

## RESULTS

Seven hundred thirty patients received naloxone for AMS (468 at Harbor-UCLA and 262 at UCLA) during the study period. Twenty-five of these patients (3.4%) were considered by the paramedics to have had a full response to naloxone, and 32 (4.4%) were considered to have had a partial or equivocal response. The remaining 673 (92.2%) were deemed nonresponders by the paramedics. Six of the 25 responders, 19 of the 32 partial responders, and 237 of the 673 nonresponders came from UCLA base; the remainder came from Harbor base. Final diagnoses at discharge from the ED, or the hospital if admitted, were obtained on all 25 responders, 26 of 32 partial responders, and 195 of 673 nonresponders. The sample of nonresponders for whom final diagnosis was obtained represented 195 of the 237 nonresponders whose prehospital care was overseen by UCLA base. The remaining 42 charts could not be located.

The percentages of patients with pinpoint pupils, with respirations of 12 or less, and with circumstantial evidence of opiate overdose were compared for the 195 nonresponders from UCLA base whose charts were obtained and a random sample of 100 nonresponders from Harbor base. Differences were small in magnitude and not statistically significant, except for the expected higher incidence of circumstantial evidence of

overdose in the Harbor base population. Because such evidence is not specific for opiate (as opposed to other drug) overdose, we do not believe that in the absence of the other elements it reflects that a greater number of patients in this group would have been found to have an ultimate diagnosis of opiate overdose had such final diagnosis been available. (Regardless, we based our further estimates of diagnostic accuracy of clinical signs in the entire nonresponder group on respirations alone or on the presence of any one of the three parameters, each of which was not significantly different for the entire group of nonresponders as for the UCLA base nonresponders with known final diagnosis.)

The sensitivity and specificity of the clinical findings in predicting a positive response to naloxone are presented (Table 1). Both pupil size (88%) and respirations of 12 or less (80%) were highly sensitive single predictors of positive response to naloxone. Twenty-four of the 25 complete naloxone responders (96%) had at least one of the three clinical indicators. The specificity of each separate clinical parameter with regard to naloxone response was at least 90%; when the three parameters were combined, the specificity was 85%.

Estimates of the sensitivity and specificity of the clinical findings in predicting a final diagnosis of opiate overdose are shown (Table 2). Although each single parameter achieves a sensitivity of approximately 75%, the presence of any one of the three criteria achieves a sensitivity of 92%.

The sensitivity and specificity of response to naloxone as predictors of final diagnosis of opiate overdose are shown for all three possible assumptions (ie, partial responders considered positive, partial responders considered negative, or those excluded) (Table 2). Because only two of the 32 partial responders were diagnosed as having had an opiate overdose, perhaps the partial responder group should optimally be treated as nonresponders; nevertheless, even with this group treated as complete responders (to maximize the sensitivity of naloxone in detecting opiate overdose), the sensitivity is only 88% (95% CI, 67% to 97%); maximum specificity is found when partial response is considered as negative, and in this case specificity equals 97% (95% CI, 94% to 99%).

**TABLE 3.** *Comparison of naloxone response and clinical findings in identifying the 24 patients with opiate overdose*

| | | Response to Naloxone | | |
|---|---|---|---|---|
| | | Positive | Negative | |
| Respirations ≤ 12 or Pinpoint pupils or Circumstantial evidence | Present | 19 | 3 | 22 |
| | Absent | 0 | 2 | 2 |
| | | 19 | 5 | 24 |
| | | $P = .25$* | | |

| | | Response to Naloxone | | |
|---|---|---|---|---|
| | | Positive | Negative | |
| Respirations ≤ 12 | Present | 18 | 3 | 21 |
| | Absent | 1 | 2 | 1 |
| | | 19 | 5 | 24 |
| | | $P = .61$* | | |

*McNemar's test of the null hypothesis that the two methods are equivalent.

Every single naloxone responder with a final diagnosis of opiate overdose had at least one of the three clinical findings, and all but one had respirations of 12 or less (Table 3). Thus, the sensitivity of clinical findings for a final diagnosis of opiate overdose is not increased by the addition of positive response to naloxone, whereas the specificity is dramatically decreased.

Six of the 25 complete responders to naloxone (24%) ultimately were proven to have had false-positive responses, as they were not ultimately given a diagnosis of opiate overdose. In four of these patients, the acute episode of AMS was related to a seizure, whereas in two, it was due to head trauma; in none of these cases did the ultimate diagnosis include opiates or any other class of drug overdose (which might have responded directly to naloxone). Thus, what was apparently misinterpreted as a response to naloxone in these cases appears in retrospect to have been due to the natural lightening that occurs with time during the postictal period or after head trauma.

## DISCUSSION

Of 730 patients receiving naloxone in the field for AMS, only 25 (3.4%) were considered to have had an unequivocally positive response. A larger number (32 patients) were considered to have had a partial or equivocal response. Taken together, only 57 of the 730 patients (7.8%), or approximately one patient in 14, had any response to the drug. If only the responders to naloxone ultimately diagnosed as having opiate overdose are considered, the frequency of true-positive response decreases to 2.9%, or about one patient in 35. Thus, even in an area in which opiate abuse is higher than the national norm, the large majority of all AMS patients will have absolutely no response to naloxone, and ever fewer patients will manifest the unequivocal response that occurs because of reversal of opiate overdose.

It is apparent in our study population that it is possible to use easily obtained clinical parameters to select a group of patients who are more likely to respond to naloxone (Table 1) and more likely to have a final diagnosis of opiate overdose (Table 2) while maintaining a high sensitivity for each of these conditions. Furthermore, these data suggest that the clinical parameters are as good or better than naloxone in correctly diagnosing the presence or absence of opiate intoxication (Table 2). Easily determined clinical indicators detected 22 of the 24 patients in our study diagnosed as having an opiate overdose, whereas only 21 of them had any response to naloxone (and only 19 had a complete response). The two patients with opiate overdose who were not identified by these clinical findings did not respond to naloxone, suggesting that serial administration of these tests fails to improve sensitivity over that achieved through the use of the clinical findings alone. The study indicates that there is no diagnostic benefit derived from the administration of naloxone to all AMS patients.

In addition, response to naloxone created a substantial amount of diagnostic confusion, as not only were there several false-positives among the complete responders (who fortu-

**TABLE 4.** *Expected performance of three strategies for administering naloxone to patients with AMS*

| | Administration Strategy | | | | | |
|---|---|---|---|---|---|---|
| | All Patients* | | Any One of Three† | | Respirations ≤ 12‡ | |
| | N | % | N | % | N | % |
| Number of patients who would receive naloxone | 730/730 | 100.0 | 177/730 | 24.2 | 56/730 | 7.7 |
| Number with complete response to naloxone | 25/730 | 3.4 | 24/177 | 13.6 | 20/56 | 35.7 |
| Number with equivocal response to naloxone | 32/730 | 4.4 | 10/177 | 5.6 | 1/56 | 1.8 |
| Number with no response to naloxone | 673/730 | 92.2 | 143/177 | 80.8 | 35/56 | 62.5 |

Naloxone is administered to *all patients with AMS, †AMS patients with respirations ≤ 12 or pinpoint pupils or circumstantial evidence of overdose, and ‡AMS patients with respirations ≤ 12.

**TABLE 5.** *Positive and negative predictive values and accuracy of selected clinical findings in populations in which opiate overdose represents 1%, 5%, and 10% of AMS patients*

| | Prevalence of Opiate Overdose in Patients With AMS | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | 1% | | | 5% | | | 10% | | |
| | PPV | NPV | ACCU | PPV | NPV | ACCU | PPV | NPV | ACCU |
| Respirations ≤ 12 | 0.12 | 1.00 | 0.94 | 0.41 | 0.99 | 0.93 | 0.59 | 0.98 | 0.93 |
| Any clinical finding | 0.04 | 1.00 | 0.76 | 0.17 | 0.99 | 0.77 | 0.30 | 0.99 | 0.78 |
| Positive response to naloxone | 0.06 | 1.00 | 0.86 | 0.25 | 0.99 | 0.86 | 0.41 | 0.98 | 0.86 |

itously awoke around the time the naloxone was administered) but also the number of equivocal responders to naloxone was greater than either the number of complete responders or even the total number of patients with opiate overdose. If the clinician interprets these equivocal responses as evidence of opiate overdose, he will be misclassifying most of these patients; interpreting partial response as evidence against opiate overdose further decreases the sensitivity of response to naloxone. Finally, treating partial response as "indeterminate" excludes naloxone response as a potential tool in a group even larger than the small group of opiate overdoses for whom this diagnostic challenge with naloxone is supposed to provide potential benefit (Table 2).

Our study design, with incomplete sampling of the nonresponders, does not permit precise calculation of the total number of patients with each of the clinical parameters or of all patients with and without a final diagnosis of opiate overdose. Nevertheless, if we assume that the patients for whom we do not have complete information (42 patients at UCLA base and 342 patients at Harbor base for whom we do not have a final diagnosis, and 336 nonresponders from Harbor base for whom we do not have clinical parameters) were similar to the entire group in each of these regards, we can make some other predictions about using various strategies to decide which patients should receive naloxone (Table 4). We know the number of patients with a final diagnosis of opiate intoxication for all 25 full responders (19 of 25), 26 of 32 partial responders (two of 26), and 195 of 673 nonresponders (three of 195). If the patients for whom final diagnoses were obtained are representative of all patients in the study, there would have been an additional 0.46 partial responders and an additional 7.35 nonresponders with a final diagnosis of opiate overdose; thus, a reasonable estimate of the prevalence of opiate intoxication in our sample is 32 of 730 (4.4%).

Similar calculations are used (Table 4) and demonstrate that either strategy of selective naloxone administration dramatically decreases the total number of patients receiving the drug while markedly increasing the percentage of complete responders among those to whom it would be given (from 3.4% to as high as 35.7% in patients with respirations of 12 or less). In addition, these strategies also decrease the number of patients who would have a partial (and thus diagnostically confusing) response to this agent. Finally, the percentage as well as absolute number of patients receiving the drug with no possible benefit (negative responders) are similarly greatly diminished, particularly with the strategy of naloxone administration only in the presence of bradypnea.

Had naloxone been administered only to those patients who had exhibited one of the three clinical indicators, the number of patients receiving the drug would have decreased from 730 to roughly 177 (24.2%). Included in these 177 patients are 24 of the 25 patients who had complete responses to naloxone (and all of the 22 naloxone responders with an ultimate diagnosis of opiate overdose), and ten of the 32 patients who had partial or equivocal responses (including both patients from this group with opiate overdose). Thus, the number of doses of naloxone administered in this study could have been reduced by more than 75% by limiting prehospital use of the drug to AMS patients with either pinpoint pupils, respirations of 12 or less, or circumstantial evidence of drug overdose, while still treating 96% of the positive responders to naloxone and 100% of the patients who had both a positive response to naloxone and a final diagnosis of opiate overdose (Table 4).

An alternate strategy would have paramedics administer naloxone only to patients with respirations of 12 or less. While this strategy would have failed to detect four of the naloxone responders, only one of these four patients was ultimately diagnosed as having opiate overdose (Table 3). This small decrease in sensitivity is substantially offset by a further increase in specificity, and the total number of patients receiving naloxone would be decreased to only 56, or 7.7% of the patients who actually received the drug (Table 4).

A strategy of administering naloxone only to patients with respira-

tions of 12 or less would have detected 20 of the 32 patients assumed to have a final diagnosis of opiate overdose (79%) as well as 18 of the 19 (95%) opiate overdose patients who responded to naloxone (Table 3) while reducing the number of patients receiving the drug by more than 90% (Table 4). Not only would this strategy have eliminated the need to give naloxone to nine of every ten AMS patients, it would also have reduced the number of partial responses from 32 to one and decreased the number of false-positive complete responders from six to two.

We strongly advocate this strategy of limiting the prehospital administration of naloxone to those AMS patients with respirations of 12 or less. While this approach may on rare occasions exclude a patient with opiate overdose who would respond to naloxone, no harm will be done by delaying diagnosis and/or treatment until such patients arrive in the ED; at the same time, the total number of patients receiving naloxone in the field without any possible benefit will be maximally limited. While the value of subsequent administration of naloxone in the ED has never been formally analyzed (and cannot be fairly evaluated on the basis of our data), allowing physicians to selectively decide which patients with AMS should receive this drug would undoubtedly retain many of the benefits demonstrated here while allowing medical judgment to determine if any other patients without clear-cut indications might still benefit from its use.

The performance of the three strategies (naloxone to all, naloxone to patients with at least one clinical indicator, and naloxone only to those with respirations of 12 or less) for areas in which the prevalence of opiate overdose in the population of patients with AMS varies from 1% (an area in which opiate overdose is uncommon) to 5% (an area similar to that found in this study) and 10% (an area in which opiate abuse is extremely high) is examined in Table 5; once again, it is assumed that patients for whom final diagnosis is known are representative of the entire study group. At each prevalence, the negative predictive value of absence of bradypnea (for ultimate diagnosis of opiate overdose) is high (at least 98%), meaning that in each of these populations almost no patients with opiate overdose would be denied naloxone if the drug were limited to patients with decreased respirations. Similarly, while even at the highest prevalence many patients with decreased respirations would prove not to have an ultimate diagnosis of opiate overdose, response to naloxone remains an even poorer positive predictor of this diagnosis regardless of prevalence. Respirations also perform at least as well as response to naloxone with regard to total accuracy at each prevalence.

Several potential problems with this study merit discussion. Threats to the internal validity of the study arise primarily from our use of a hybrid study design. Had it been possible to obtain a final diagnosis for all 730 patients, no assumptions regarding the representativeness of the nonresponder sample would be required, and estimates of the sensitivity and specificity of naloxone and the clinical indicators in detecting opiate overdose would be more accurate. In addition, the exact number of patients with a final diagnosis of opiate intoxication would be known, and direct estimation of the disease prevalence and associated parameters would have been possible. Furthermore, the sample size for many of the sensitivity and specificity calculations would increase, resulting in more precise estimates of these parameters and increased discriminatory power.

Fortunately, the potential problems created by the use of sampling in the nonresponder population do not threaten our conclusions. It is in fact likely that due to sampling bias we have overestimated the sensitivity and specificity of response to naloxone in predicting a final diagnosis of opiate overdose. There were six partial responders and 478 nonresponders for whom final diagnosis was not obtained. A few of these patients (roughly eight if the sampled patients are representative of the entire group) are likely to have had a final diagnosis of opiate overdose; because none of these patients responded to naloxone, inclusion of these "uncounted" patients would decrease the sensitivity of naloxone.

Depending on how many of the uncounted cases of opiate intoxication had positive clinical indicators, the sensitivity of these clinical findings could increase, decrease, or remain unchanged. At worst, if clinical indicators were present in none of the uncounted cases, the decrease in sensitivity would be of the same size as the decrease in naloxone sensitivity. Thus, the bias in the sensitivity measurements is such that it underestimates the sensitivity of the clinical parameters relative to the sensitivity of naloxone, providing additional support for our contention that the clinical indicators are as good or better than naloxone response in identifying patients with opiate intoxication.

There are several potential threats to the external validity of this study. It could be argued that the paramedics may have incorrectly classified the patient's response to naloxone or the value of the clinical findings. Although this may be true, there is no reason to believe that the performance of Los Angeles paramedics is any different from that of paramedics in other parts of the country, and these classification errors are inherent in any such program. Furthermore, concern regarding paramedic errors is further reason to advocate delaying the administration of naloxone until the patient arrives in the ED (hypoventilating patients excepted).

Final diagnosis in this study is based on a physician's discharge diagnosis. The workup that led to this diagnosis and the criteria for making a diagnosis of opiate intoxication were solely at the discretion of the treating physician. No attempt was made to mandate or obtain toxicologic confirmation of the diagnosis. Had the primary purpose of this study been to accurately establish the specificity of naloxone for opiate receptors, for example, careful toxicologic analyses would have been required. Our purpose, however, was to critically examine the current widespread strategy of empiric naloxone administration as a diagnostic tool. Because the final diagnoses in our study patients were made by physicians already aware of each patient's response to naloxone, it is likely that any errors in clinical diagnosis would have been biased such that the concordance between naloxone response and final diagnosis was enhanced. In addition, naloxone's value as a possible diagnostic tool for clinicians can be estimated only according to whether it

actually helps clinicians in their diagnostic decision making.

It is also possible that clinical parameters might perform much less well as a predictor of opiate overdose in a population with a higher percentage of mixed drug overdoses. Combinations of drugs such as codeine and glutethimide ("loads") and heroin and cocaine ("speedballs") have been described as very popular in some areas (including Los Angeles),[13,14] and it is quite conceivable that among users of these drugs the offsetting effect of the second agent, on pupil size, for example, could hide the effect of the opiate. While this may be true, it is likely that the same confounding effect would alter the patient's response to naloxone. Thus, any circumstance tending to limit the predictive accuracy of clinical characteristics would be expected to similarly limit the diagnostic value of response to naloxone.

## CONCLUSION

We believe that there is little justification for routine empiric prehospital use of naloxone in patients with altered mental status. Our data indicate that the presumed diagnostic value of response to naloxone as a predictor of presence or absence of opiate overdose has been greatly overstated and that easily determined clinical parameters perform at least as well in this regard. Limiting administration of naloxone to patients with clinical predictors of opiate overdose would save money and decrease the likelihood of adverse effects from the drug while also decreasing the diagnostic confusion created by equivocal responses in a substantial subset of patients. The strategy of administering naloxone only to AMS patients with bradypnea (respirations of 12 or less) would target the drug to a population for whom there is a substantial possibility of benefit.

## REFERENCES

1. Epstein FB, Eilers MA: Poisoning, in Rosen P, Baker FJ, Barkin RM, et al (eds): *Emergency Medicine.* St Louis, CV Mosby Co, vol 2, 1988, p 330.

2. Rappolt RT, Gay GR, Decker WJ, et al: NAGD regimen for the coma of drug-related overdose. *Ann Emerg Med* 1980;9:357-363.

3. Ellenhorn MJ, Barceloux DG: *Medical Toxicology: Diagnosis and Treatment of Poisoning.* New York, Elsevier Science Publishing Co, Inc, 1988, p 752.

4. Schwartz JA, Koenigsberg MD: Naloxone-induced pulmonary edema. *Ann Emerg Med* 1987;16:1294-1296.

5. Pallasch TJ, Gill CJ: Naloxone-associated morbidity and mortality. *Oral Surg* 1981;52:602-603.

6. Prough DS, Roy R, Bumgarner J: Acute pulmonary edema in healthy teenagers following conservative doses of intravenous naloxone. *Anaesthesia* 1984; 60:485-486.

7. Hansen HJ, Caudill SP, Boone J: Crisis in drug testing: Results of CDC blind study. *JAMA* 1985;253: 2382-2387.

8. Ingelfinger JA, Isakson G, Shine D, et al: Reliability of the toxic screen in drug overdose. *Clin Pharmacol Ther* 1981;29:570-575.

9. Schwartz RH: Urine testing in the detection of drugs of abuse. *Arch Intern Med* 1988;148:2407-2412.

10. Griner PF, Mayewski RJ, Mushlin AI, et al: Selection and interpretation of diagnostic tests and procedures: Principles and applications. *Ann Intern Med* 1981;94:559-563.

11. Fleiss JL: *Statistical Methods for Rates and Proportions,* ed 2. New York, John Wiley & Sons, 1981, p 14-15.

12. Armitage P, Berry G: *Statistical Methods in Medical Research,* ed 2. Oxford, Blackwell Scientific, 1987, p 120-121.

13. Khajawall AM, Sramek JJ: "Loads alert." *West J Med* 1982;137:166-168.

14. Cohen S: Cocaine. *JAMA* 1975;231:74-75.