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Dose-dependent Reduction of the Minimum Local Analgesic Concentration of Bupivacaine by Sufentanil for Epidural Analgesia in Labor

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Background: **The minimum local analgesic concentration (MLAC) has been defined as the median effective local analgesic concentration in a 20-ml volume for epidural analgesia in the first stage of labor. The aim of this study was to determine the local anesthetic-sparing efficacy of epidural sufentanil by its effect on the MLAC of bupivacaine.**

Methods: **In this double-blind, randomized, prospective study, 147 parturients at ≤7 cm cervical dilation who requested epidural analgesia were allocated to one of four study groups. After a lumbar epidural catheter was placed, study participants received 20 ml bupivacaine (n = 38), bupivacaine with sufentanil 0.5 μg/ml (n = 38), bupivacaine with sufentanil 1 μg/ml (n = 33), or bupivacaine with sufentanil 1.5 μg/ml (n = 38). The concentration of bupivacaine was determined by the response of the previous patient using up-down sequential allocation. The analgesic efficacy was assessed using 100-mm visual analog pain scores, with ≤10 mm within 30 min defined as effective.**

Results: **The MLAC of bupivacaine alone was 0.104% wt/vol (95% CI, 0.090–0.117). The addition of sufentanil at doses of 0.5 μg/ml, 1 μg/ml, and 1.5 μg/ml resulted in significant reductions ($P < 0.0001$) in the MLAC of bupivacaine to 0.048% wt/vol (95% CI, 0.030– 0.065), 0.021% wt/vol (95% CI, 0–0.055), and 0.009% wt/vol (95% CI, 0–0.023), respectively.**

Conclusions: **This study showed a significant ($P < 0.0001$) dose-dependent reduction in the MLAC of bupivacaine by sufentanil. (Key words: Analgesic potency; Dixon and Massey; epidural opioids; obstetric; pregnancy.)**

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CONCENTRATIONS of local anesthetics used for epidural analgesia in labor have been reduced with the addition of epidural opioids. To evaluate the pharmacodynamic contributions of the various epidural analgesics, we previously described a clinical model to determine the relative potencies of local anesthetic agents in the first stage of labor.[1–3] The minimum local analgesic concentration (MLAC) has been defined as the median effective local analgesic concentration (EC_{50}). This model was recently used to estimate the local anesthetic-sparing potential of epidural fentanyl.[3,4]

Dilute solutions of epidural bupivacaine combined with opioids have been used to achieve satisfactory analgesia while minimizing the unwanted local anesthetic effect of motor blockade.[5] The addition of epidural sufentanil can improve the quality of labor analgesia and may reduce the incidence of instrument-assisted deliveries without depressing the neurobehavioral status of the newborn.[6] However, the relation between varying doses of sufentanil and bupivacaine has not been quantified adequately. The aim of this study was to determine the local anesthetic-sparing efficacy of epidural sufentanil by its effect on the MLAC of bupivacaine.

Materials and Methods

This research was conducted at the University of Michigan Medical Center, Ann Arbor. After we received approval from the institutional review board and written informed patient consent, we enrolled 147 parturients classified as American Society of Anesthesiologists physical status 1 and 2 who requested epidural analgesia. Participants had singleton pregnancies at >36 weeks' gestation with vertex fetal presentation. All women were in active labor with cervical dilation of 3–7 cm at the time of catheter placement. Those who had received opioid or sedative medications were excluded.

After intravenous prehydration with 1,000 ml lactated Ringer's solution, patients were placed in the flexed sitting position. After raising a midline wheal with 1% wt/vol lidocaine, the epidural space was identified using loss of resistance to saline at L2–L3 or L3–L4, and an end-hole epidural catheter was advanced 3 cm into the epidural space. Loss of resistance to saline was used to identify entry into the epidural space. The volume of saline used was <2 ml to reduce the possibility of dilution. A lidocaine with epinephrine test dose was not used.

Participants were allocated to one of four groups in a double-blinded, randomized, prospective study design. In the first phase of the study, the bupivacaine-control group (n = 38) received 20 ml bupivacaine (bupivacaine HCl injection, USP; Abbott Laboratories, North Chicago, IL) and the experimental group (n = 38) received 20 ml bupivacaine with 1.5 μg/ml (30 μg) sufentanil (sufentanil citrate injection, USP; Elkins-Sinn, Cherry Hill, NJ). In the second phase of the study, two further experimental groups were randomized to receive bupivacaine with sufentanil at concentrations of 0.5 μg/ml (n = 38) or 1 μg/ml (n = 33). The concentration of bupivacaine received by a particular patient was determined by the response of the previous patient in that group to a higher or lower concentration using an up-down sequential allocation technique. The testing interval was 0.01% wt/vol. The first patient in each group received 0.07% wt/vol bupivacaine based on an estimate of MLAC from a previous study.[4] Each study solution was freshly prepared by the operating room pharmacist using preservative-free saline as the diluent to achieve the desired concentration at room temperature (20°C). After catheter placement, patients were placed in the supine position with left uterine displacement and 30° elevation of the head of the bed. The injectate was given within 5 min. Patients were monitored with a noninvasive blood pressure cuff, pulse oximetry, and tococardiography.

The anesthesiologist performing the procedure and subsequent assessment was blinded to the concentration used and group allocation. Efficacy of the study drug was assessed using 100-mm visual analog pain scores (VAPS) in which 0 represented no pain, and 100 was the worst possible pain at 0, 15, and 30 min after bolus injections. A VAPS of ≤10 mm was defined as effective. Three outcomes were considered.

1. Effective: A VAPS of ≤10 mm during contractions within 30 min of injection. A result defined as effective directed a 0.01% wt/vol decrement for the next patient.
2. Ineffective: A VAPS >10 mm because of pain that responded to rescue with a 12-ml bolus of 0.25% wt/vol bupivacaine. A result defined as ineffective directed a 0.01% wt/vol increment for the next patient.
3. Reject: A VAPS >10 mm because of pain that did not respond to rescue. A result defined as a reject directed that the same concentration be repeated for the next patient allocated to that group.

At 30 min, participants not defined as having effective analgesia were given the rescue bolus. Those not responsive to rescue were designated as rejects. Further management then included repeated epidural catheterization, intrathecal opioid with or without bupivacaine, or parenteral opioid as appropriate. Patients with effective bupivacaine analgesia were given an infusion of 0.125% wt/vol bupivacaine with 2 μg/ml fentanyl after the study was completed.

Statistical Analysis

Demographic and obstetric data were collected and are presented as means (SD), medians (interquartile range), and counts as appropriate and analyzed using analysis of variance, Kruskal-Wallis, and chi-squared tests, respectively. The median effective concentrations were estimated from the up-down sequences using the method of Dixon and Massey,[7] which allowed MLACs with 95% confidence intervals to be derived. The dose-response effects of sufentanil were examined using analysis of variance with Bartlett's test for homogeneity of variance. Analyses were done using the following software: Excel 5.0a for Windows (Microsoft Corp., Redmond, WA), Statistical Package for the Social Sciences 6.1 for Windows (SPSS, Inc., Chicago, IL), and GraphPad Instat (GraphPad Software, San Diego, CA) 2.05a for DOS. Statistical significance was defined for overall alpha errors at the 0.05 level. All probability values were two sided, with multiple comparison corrections applied as appropriate.

Sample size estimations were based on the results of a previous study that showed that the MLAC of bupivacaine was 0.069% (SD, 0.028).[4] A conservative threshold alpha error of 0.016 was applied to allow for multiple comparisons to maintain the overall alpha error at the 0.05 level. Power was given at 0.8, with the minimum difference to be significant as a 50% reduction in the MLAC of bupivacaine by sufentanil. It was then esti-

Table 1. Demographic and Obstetric Data

	Bupivacaine–Control	Bupivacaine–Sufentanil		
		0.5 μg/ml	1.0 μg/ml	1.5 μg/ml
Age (yr)	27.4 (4.87)	28.8 (4.52)	28.3 (6.23)	29.1 (5.17)
Height (cm)	163.3 (7.81)	166 (5.44)	165.8 (6.45)	165.1 (6.28)
Weight (kg)	81.5 (15.46)	82.9 (13.75)	80.1 (8.78)	81.4 (13.92)
Gestation (wk)	40 (1.45)	40 (0.96)	39.8 (1.33)	39.7 (1.29)
Cervical dilatation (cm)	4.2 (0.99)	4.3 (1.24)	4.2 (1.39)	4.3 (1.03)
Nulliparous	19	17	10	17
Oxytocin	12	13	17	12
Initial VAPS (mm)	83 [71–92]	81 [71–90]	80 [69–90]	79 [70–85]

Results are expressed as mean (SD), median [interquartile range], and count as appropriate.

VAPS = visual analog pain score.

mated that a minimum of 28 women would be required per group.

Results

There were no significant demographic, obstetric, or hemodynamic differences among the four groups (tables 1 and 2). No woman had a systolic blood pressure <100 mmHg, oxygen saturation <94%, or pruritus requiring treatment during the study period. One participant in the 1.5 μg/ml sufentanil group had a transient fetal heart rate reduction from 130 beats/min to 105 beats/min that responded to improved left uterine displacement and intravenous fluid infusion. Of the 147 women enrolled in the study, 27 were designated as rejects (table 3), leaving 30 patients in each of the four groups for analysis. Figure 1 shows the sequences of effective and ineffective analgesia. The dose-dependency effect of sufentanil (analysis of variance, $P < 0.0001$) was associated with a significant difference in variance in the groups using Bartlett's test ($P < 0.0001$). The data were subsequently analyzed using Kruskal-Wallis nonparametric one-way analysis ($P < 0.0001$) with Dunn's *post hoc* tests and Cuzick's test for rank trend.[8] There were significant dose-dependent reductions in the MLAC of bupivacaine ($P < 0.001$) with 0.5 μg/ml, 1 μg/ml, and 1.5 μg/ml sufentanil compared with the bupivacaine control (table 4). This was also demonstrated by a significant rank trend ($P < 0.0001$) to reducing the MLAC of bupivacaine with increasing sufentanil doses.

Discussion

The Minimum Local Analgesic Concentration Model

There has been a tendency to reduce the concentrations of local anesthetics used for epidural analgesia in labor. Further reduction of the local anesthetic concentrations has been possible with the addition of other epidural analgesics, such as opioids and clonidine.[9,10] Many studies have described and compared various regimens for providing epidural analgesia.[11,12] It has been difficult, however, to determine the contribution of each drug to the overall efficacy of the analgesia. Studies comparing the efficacies of epidural analgesics have been limited by the lack of knowledge of the relative potencies of the involved agents, whether alone or in combination. The anesthetic potencies of volatile agents have been quantified in terms of minimum alveolar concentration, and the same concept can be applied to

Table 2. Hemodynamic Data

	Bupivacaine–Control	Bupivacaine–Sufentanil		
		0.5 μg/ml	1.0 μg/ml	1.5 μg/ml
Lowest maternal SBP (mmHg)	122.8 (12.08)	122.3 (10.96)	122.4 (13.27)	122.4 (8.73)
Lowest maternal HR (bpm)	80.6 (14.56)	79.7 (15.27)	76.5 (13.46)	76 (9.02)
Lowest FHR (bpm)	129.8 (7.39)	131.7 (8.39)	129.3 (9.90)	130.4 (9.79)

Results are expressed as mean (SD) and count as appropriate.

SBP = systolic blood pressure; HR = heart rate; FHR = fetal heart rate.

Table 3. Distribution of Rejects

Bupivacaine (% wt/vol)	Bupivacaine–Control	Bupivacaine–Sufentanil 0.5 μg/ml	Bupivacaine–Sufentanil 1.0 μg/ml	Bupivacaine–Sufentanil 1.5 μg/ml
0.12	1(C)			
0.11	1(C)			
0.10	2(A) 1(B)			
0.09				
0.08				
0.07		2(A)	1(B)	
0.06	1(A) 2(C)	1(A) 1(B)		
0.05		1(A) 1(C)		
0.04				
0.03				
0.02		2(A)		2(C)
0.01			1(B)	2(A) 2(B)
0			1(C)	2(A)

A = VAPS > 10 mm due to pain that fails to respond to rescue; B = protocol violation; concentration repeated; C = second stage of labor prior to study completion; concentration repeated.

epidural analgesics. The MLAC model allows the estimation of the epidural analgesic EC_{50} of local anesthetics in the first stage of labor and also the effect of the addition of opioids by its effect on the MLAC as the dependent variable.

Methods

Some aspects of the study methods require further explanation. Although EC_{95} is more clinically relevant, we concluded that an estimation of EC_{50} would provide a more sensitive research tool due to the respective positions of each on the cumulative concentration-response curve.[1] The EC_{50} corresponds to the inflection point where the slope is greatest. Parturients who had cervical dilation >7 cm were excluded to minimize the loss of women from the study because of the approach of the second stage of labor with the onset of perineal pain outside the T10 to L1 distribution. Loss of resistance to saline was used to identify entry into the epidural space to minimize the incidence of unblocked segments, which may occur with the loss-of-resistance-to-air technique.[13] Omission of a lidocaine test dose was essential to eliminate any analgesic effect of the lidocaine. A 20-ml bolus was used so volume would not be a limiting factor in achieving adequate spread. The use of a 12-ml bolus with the patient in the sitting position has been shown to result in an upper sensory level only to T10 in some patients.[14] Because the EC_{50} was to be estimated, we decided to be exact and only accept VAPS of ≤10 mm as effective. Brownridge[15] has shown that intervention is requested when VAPSs exceed 30 mm.

The up-down sequential allocation technique, rather than random allocation, was chosen because of the ease with which it estimates the EC_{50} of a sample. This technique has been used to determine dose-response phar-

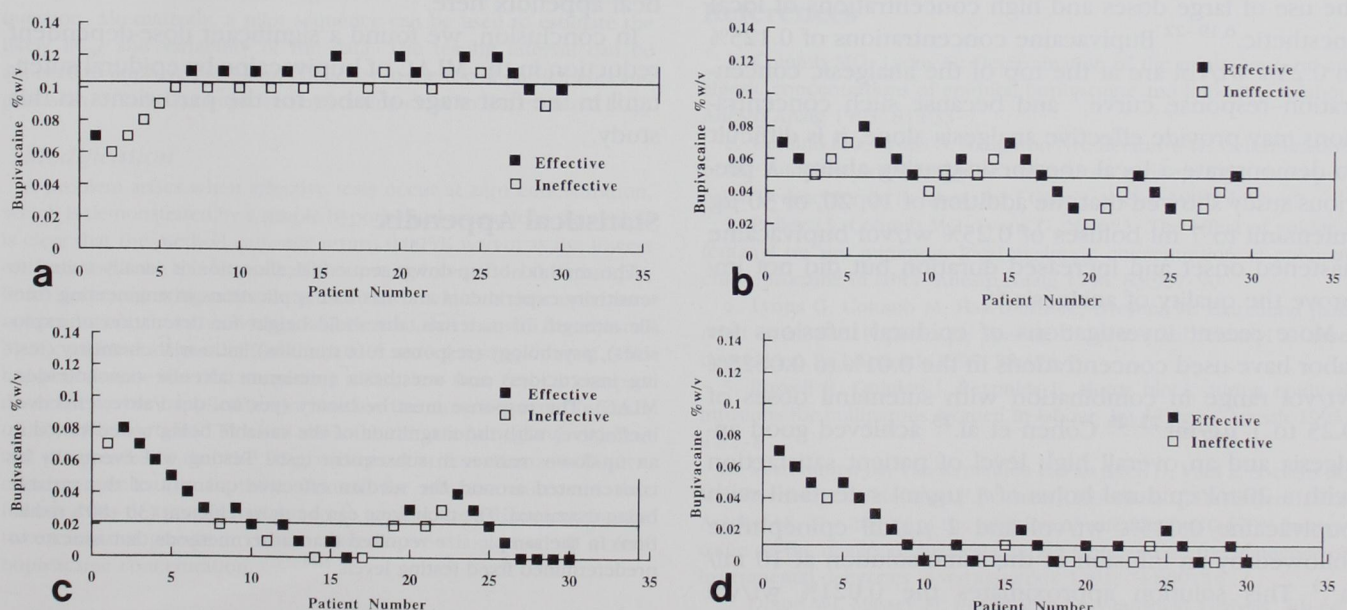

Fig. 1. The median effective local analgesic concentration of bupivacaine, and with addition of sufentanil 0.5, 1, and 1.5 μg/ml as determined by the technique of up-down sequential allocation. The minimum local analgesic concentrations are 0.104, 0.048, 0.021, and 0.009% wt/vol, respectively. Error bars represent the 95% confidence interval. The testing interval was 0.01% wt/vol.

Table 4. Results

Group Allocation	MLAC [% wt/vol (95% CI)]	Dunn's *P**
Bupivacaine–control	0.104 (0.090–0.117)	
Bupivacaine–sufentanil 0.5 μg/ml	0.048 (0.030–0.065)	<0.001
Bupivacaine–sufentanil 1.0 μg/ml	0.021 (0–0.055)	<0.001
Bupivacaine–sufentanil 1.5 μg/ml	0.009 (0–0.023)	<0.001

MLAC of bupivacaine and sufentanil concentrations, compared with MLAC of control.

MLAC = minimum local analgesic concentration; CI = confidence interval.

* *P* values against bupivacaine control: Kruskal-Wallis analysis, KW = 83.07, $P < 0.0001$; Cuzick's test for rank trend, $P < 0.0001$.

macodynamics for both inhalational and intravenous anesthetics.[16–18]

In the first phase of the study, some patients did not require any local anesthetic and experienced effective analgesia with sufentanil alone. Because such a profound effect was observed with the addition of 1.5 μg/ml sufentanil, a second phase of the study was initiated using 0.5 μg/ml and 1.0 μg/ml sufentanil concentrations.

Bupivacaine and Sufentanil in Combination

Initial studies of the combination of epidural sufentanil and bupivacaine for labor analgesia were hindered by the use of large doses and high concentrations of local anesthetic.[6,19–22] Bupivacaine concentrations of 0.125% to 0.25% wt/vol are at the top of the analgesic concentration-response curve,[1] and because such concentrations may provide effective analgesia alone, it is difficult to demonstrate a local anesthetic-sparing ability. A previous study showed that the addition of 10, 20, or 30 μg sufentanil to 7 ml boluses of 0.25% wt/vol bupivacaine hastened onset and increased duration but did not improve the quality of analgesia.[22]

More recent investigations of epidural infusions for labor have used concentrations in the 0.01% to 0.0625% wt/vol range in combination with sufentanil doses of 0.25 to 1 μg/ml.[23–25] Cohen et al.[23] achieved good analgesia and an overall high level of patient satisfaction with a 20-ml epidural bolus of 1 μg/ml sufentanil with bupivacaine 0.015% wt/vol and 2 μg/ml epinephrine followed by an infusion of the same solution at 10 ml/h.[23] This solution approximates the 0.021% wt/vol MLAC of bupivacaine, which resulted from the addition of 1 μg/ml sufentanil in this study. Our finding that 1.5 μg/ml sufentanil alone provided effective analgesia in some patients also corresponds with the results of previous research.[26]

Other investigators have shown the local anesthetic-sparing ability by comparing fixed-dose regimens and calculating the total milligrams of bupivacaine use by infusion, repeated epidural injections, or both.[6,20–22,27] The addition of sufentanil to bupivacaine increases analgesic duration and thereby widens the interval between repeated epidural injections, which results in reduced total milligrams of bupivacaine used during the course of labor. In contrast, the MLAC method shows the spontaneous interaction in which the bupivacaine concentration is allowed to fluctuate as the dependent variable. This novel approach quantifies the local anesthetic-sparing ability in terms of a bupivacaine concentration in addition to the total dose delivered.

If a bupivacaine–sufentanil combination is to be used clinically, it is important to realize that MLAC, although an ED_{50}, represents a higher standard of analgesia than clinically required in labor. Therefore, in considering previously published research, it would seem reasonable that the clinical use of MLAC bupivacaine with the sufentanil doses studied is a rational approach.

Statistical Analysis

A discussion of up-down sequential allocation, including a modification to the analysis, aspects of study design, and other statistical issues, is offered in the statistical appendix here.

In conclusion, we found a significant dose-dependent reduction in the MLAC of bupivacaine by epidural sufentanil in the first stage of labor for the parturients in this study.

Statistical Appendix

The method of up-down sequential allocation is ideally suited to sensitivity experiments and has had applications in engineering (tensile strength of materials, threshold height for detonation of explosives), psychology (response to a stimulus), industrial chemistry (testing insecticides) and anesthesia (minimum alveolar concentration, MLAC). The response must be binary (yes/no, dead/alive, effective/ineffective) with the magnitude of the variable being tested varied in an up-down manner in subsequent tests. Testing will eventually be concentrated around the median effective quantity of the variable being examined. The technique can be more efficient (30–80% reduction) in the sample size required than other methods that allocate to predetermined fixed testing levels.[7,28]

Median Effective Concentration

The EC_{50} can be estimated using the Dixon and Massey method.[7] In our MLAC studies, the average of the concentrations is taken for the

tests involving the outcome that occurs less frequently. If these are ineffective tests, then that average is adjusted by the addition of one half the testing interval to yield the EC_{50}. The average of the effective tests, if taken, therefore would be adjusted by subtracting the same quantity.

Precision of the Estimate

Estimation of the precision (SEM, 95% CI) of the EC_{50} has prompted some debate. Intuitively it would appear reasonable to use standard regression methods using probit or logit transformations. However, because the concentration tested on any participant depends on the result from the previous participant, the independence of observations has been questioned, which is a basic assumption of regression analysis. It is possible that a concentration being tested might induce bias in participant selection or outcome expectation. Therefore the enrollment of participants and assessment of efficacy should be blinded to the concentration being tested and the status of the up-down sequence. In addition, by using two or more simultaneous sequences, participants can be randomized to particular groups representing differing interventions. Dixon and Massey[7] describe an alternative method to regression techniques, and readers are encouraged to read their text for a full description.

Sample Size

Estimation of the sample size required for the up-down technique is similar to usual calculations, except that approximately twice the number of participants would be required. This is because the estimates of EC_{50}, SEM, and 95% CI are based on the number and distribution of the outcome that occurs less frequently, which will be approximately 50% of the observations.

Testing Interval

If prior information is available, the method will be efficient if the testing interval is within the range of 0.5 to 2 SD for the variable in question. Alternatively, a pilot sequence can be used to estimate the likely EC_{50} and variability of the data. The testing interval can be adjusted to improve precision. Efficiency in the use of participants and precision will also be improved by starting close to the eventual EC_{50}.

Modification

A problem arises when effective tests occur at zero concentration, which is demonstrated by a simple hypothetical example in figure 2. It is clear that the method can only return 0.005% wt/vol as the lowest estimate, because this is one half the testing interval. In the example, if the lesser occurring outcome is ineffective, which is the case at zero concentration, then the average will be zero and this will be adjusted by the addition of one half of the 0.01% wt/vol testing interval. This happens despite the data suggesting a EC_{50} less than zero. A compromise that we have applied before is to use the more frequent outcome, usually effective tests.[4] This can allow the return of a negative estimate and the possibility that the EC_{50} will occur at less than zero bupivacaine concentration. In these studies, the effective outcomes that followed the first ineffective test were used in the estimations for the two sufentanil groups in which effective tests occurred at a zero bupivacaine concentration.

Variability

There was a significant difference ($P < 0.0001$ by Bartlett's test) in variances in the groups detailing the dose-dependency effect of sufentanil, which breaks a required assumption for the use of parametric analysis of variance. This may be explained in part by the censoring effect of reaching zero concentrations for bupivacaine on variance. A similar study using fentanyl with bupivacaine revealed homogeneity of variance.[4] However, it is possible that the response to sufentanil is subject to differing variances, and because the samples are often the only information available, further consideration may be warranted. Because it is not possible *post hoc* to perform suitable transformations for the method of Dixon and Massey (because of the fixed testing interval), a distribution-free Kruskal-Wallis analysis was applied.

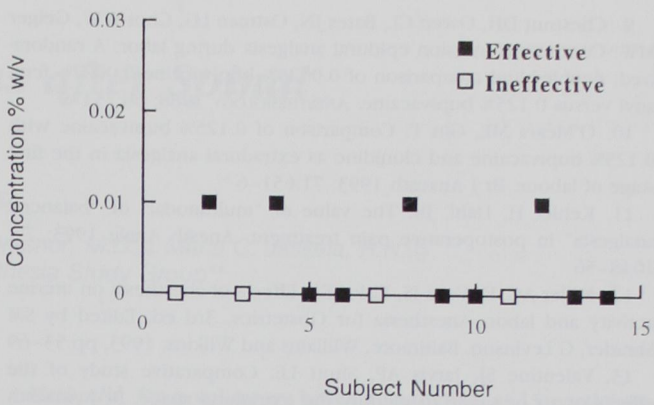

Fig. 2. In this hypothetical example, the median effective concentration appears to be better estimated by taking the more frequent outcome, effective tests. Calculation template: Average of tests ± the half testing interval = EC_{50}. Ineffective tests: (0 × 4)/4 + (0.01)/2 = 0.005% wt/vol. Effective tests: [(0.01 × 4) + (0 × 6)]/10 − (0.01)/2 = −0.001% wt/vol.

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