Medical Intelligence Article

Patient-Controlled-Analgesia Analgesimetry and Its Problems

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In addition to providing pain relief, patient-controlled-analgesia (PCA) is also extensively used in clinical research for the assay of analgesic effectiveness of new drugs and methods of pain treatment. The main outcome measure of PCA analgesimetry is the difference in opioid requirements between the control (placebo) group and the new drug (or treatment) group. The following potential problems of PCA analgesimetry are analyzed: 1) weak correlation between pain intensity and opioid consumption, 2) interference of nonanalgesic effects of opioids, 3) role of acute tolerance to the analgesic effect of opioids, 4) problems of the patient's training, 5) interaction between main outcome measures, and 6) sample size and negative outcome problems. Knowledge of the pitfalls of PCA analgesimetry should decrease the risk of errors in its use.
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Patient-controlled-analgesia (PCA) has gained wide acceptance as a standard method of postoperative pain management.[1,2] In addition to providing pain relief, PCA is also extensively used for the assay of analgesic effectiveness. The application of PCA for analgesimetry was suggested by Sechzer in 1968.[3] He stated that "the analgesic demand would be a measure of pain," and "new analgesic drugs and pain therapies could be evaluated by comparing respective analgesic demands in appropriately designed studies."[4] The use of PCA analgesimetry in pain studies for the assessment of new drugs and methods became very popular. The PubMed database for the combination of terms "patient-controlled analgesia" and "opioid consumption" has more than 600 clinical trials 400 of which have been published in the last 10 yr. Both patient-controlled IV analgesia and patient-controlled epidural analgesia are used for this aim, patient-controlled IV analgesia much more frequently than patient-controlled epidural analgesia.

The PCA devices used for analgesimetry most commonly deliver morphine (an incremental dose of 1.0–1.5 mg, lockout interval of 7–10 min, and 4-h limit of 30–40 mg); however, other opioids (fentanyl, alfentanil) are also used. The PCA main outcome measure is the difference in opioid requirements between the control (placebo) group and the new drug (or treatment) group. The other outcome measures include pain intensity score (usually visual analog scale) and frequency of electronic demands for the incremental dose of an opioid. Level of sedation and side effects profile are also included in the PCA studies.

PCA analgesimetry has been used for various types of studies, not only for assessment of the analgesic effect of new drugs. It is used for evaluation of such treatment modalities as nerve blocks and transcutaneous electrical nerve stimulation or for confirming new concepts such as preemptive analgesia. It is widely used for assessment of various drug combinations and multimodal approaches to the treatment of pain. Among various groups of analgesic drugs studied with the use of PCA analgesimetry, nonsteroidal antiinflammatory drugs (NSAIDs) are the most prominent. Of the 600 clinical trials mentioned above, more than 100 were devoted to the assessment of NSAIDs. Table 1 presents ketorolac as an example of NSAID studies listing only randomized, double-blind, and placebo-controlled studies. Of the 11 publications, nine reported that ketorolac produced a statistically significant decrease in opioid requirements, in five of them the pain score was also decreased (compared with the placebo group). However, in four studies the changes in pain intensity were not statistically significant. One of the important features revealed by the table is wide variability in the decrease of opioid consumption (from 0% to 50%) at similar dose ranges. The other is that in many studies the difference between the treatment group and placebo group is not

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Table 1. PCA Analgesimetry with Ketorolac: Randomized, Double-Blind, and Placebo-Controlled Studies in Postoperative Pain

Reference	Procedure	Ketorolac administration	PCA regimen (increments–mg, lockout–min)	Sample size (keto/placebo)	Morphine consumption (change from control)	Pain score (change from control)
Gillies et al.[5]	Upper abdominal surgery	Continuous IM infusion 3.0 mg/h for 24 h, total 72 mg	Morphine ≈1.2 mg 2 min	20/20	↓ 29% $P < 0.06$	↓ $P < 0.05$
Burns et al.[6]	Upper abdominal surgery	Continuous IM infusion 12.5 mg/h for 30 min plus 2 mg/h for 24 h, total 60 mg	Morphine ≈1.3 mg 2 min	18/21	↓ 49% $P < 0.001$	NS
Sevarino et al.[7]	Intraabdominal gynecologic surgery	Five IM doses, 60 mg plus four doses of 30 mg, total 180 mg for 24 h	Morphine ≈1 mg 6 min	12/11	↓ 48% $P < 0.05$	NS
Blackburn et al.[8]	Abdominal hysterectomy	Continuous IV infusion for 24 h, total 120 mg	Morphine ≈1 mg 5 min	30/29	↓ 21% $P = 0.02$	↓ $P = 0.04$
Rogers et al.[9]	Abdominal hysterectomy	10 mg IV before surgery	Diamorphine 1 mg 5 min	30/32	? $P < 0.01$	NS
Etches et al.[10]	Total hip or knee arthroplasty	30 mg IV bolus plus continuous infusion 5 mg/h for 24 h, total 150 mg	Morphine ≈1.2 mg 6 min	86/88	↓ 44% $P < 0.001$	↓ $P < 0.001$
Fogarty et al.[11]	Total hip arthroplasty	30 mg IM every 6 h for 18 h, total 180 mg	Morphine ≈1 mg 6 min	30/30	↓ 50% $P < 0.02$	NS
Reuben et al.[12]	Spinal stabilization	15 or 30 mg IV every 6 h for 24 h, total 60 or 120 mg	Morphine ≈1.5 mg 8 min	20 per group	↓ 37% $P < 0.001$ for both doses	↓ $P < 0.001$
Ruben et al.[13]	Spinal fusion surgery	0, 5, 7.5, 10, 12.5, 15, or 30 mg every 6 h for 24 h	Morphine ≈1.5 mg 8 min	10 per group	↓ 40%–50% $P < 0.001$ for 7.5 to 30 mg doses	↓ $P < 0.05$
Alexander et al.[14]	Total hip or knee arthroplasty	60 mg IV before surgery	Morphine ≈1.0 mg 5 min	31/32	NS	NS
Wilder-Smith et al.[15]	Surgery for intervertebral disc herniation	30 mg IV before surgery	Morphine ≈1.1 mg 8 min	15/15	NS	NS

PCA = patient-controlled-analgesia; NS = not significant.

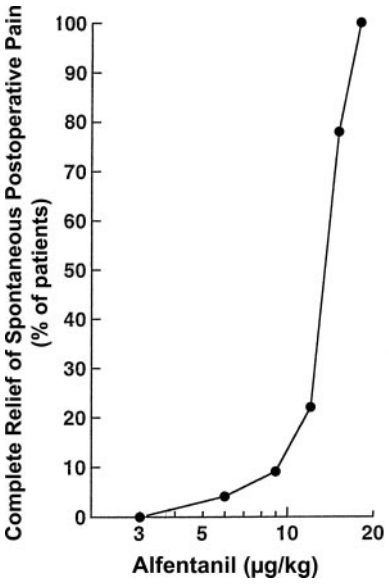

Figure 1. Cumulative frequency distribution curve for complete pain relief (23 patients). Along the horizontal axis, the cumulative doses of alfentanil (3 μg/kg, increments at 5-min intervals, IV) on a log scale. From Tverskoy et al.[16] ©Lippincott-Raven, reproduced by permission.

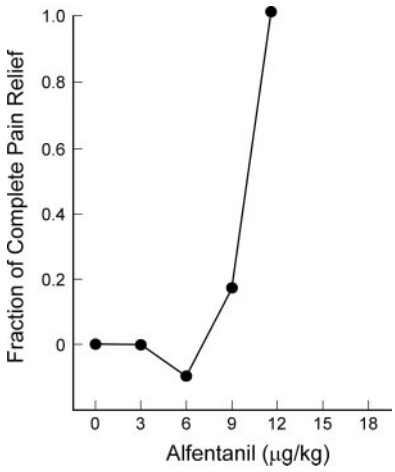

Figure 2. Individual dose-response curve for the analgesic effect of alfentanil in a patient from the group presented in Figure 1. Shown along the vertical axis is the analgesic effect in fractions of the complete pain relief, and along with horizontal axis, the cumulative dose of alfentanil.[16] From Tverskoy et al. ©Lippincott-Raven, reproduced by permission.

only in opioid consumption but also in pain intensity: the treatment group has a significantly lower pain intensity than the placebo group. Why did the study patients not (especially in the placebo group) self-administer enough opioid to provide adequate pain relief? These features are common to most of the studies with the use of PCA analgesimetry and are associated with multiple PCA problems presented below.

Weak Correlation Between Pain Intensity and Opioid Consumption

PCA analgesimetry is based on the assumption that there is a good direct relationship between pain intensity and the dose of an opioid used to provide pain relief. However, when this relationship was studied, it was found not to be strong.

Figure 1 illustrates the results of the study on alfentanil dose-response relationship in postoperative pain.[16] Patients received small (3 μg/kg, IV) increments of alfentanil at 5-min intervals. Spontaneous postoperative pain was completely relieved in all 23

patients in the study, with cumulative doses of alfentanil ranging from 6 to 18 μg/kg. The within-patient alfentanil dose-analgesic response curves were mostly quantal in nature: a precipitous decrease in pain intensity after the injection of only one of the increments. The example of the dose-response curve in an individual patient is in Figure 2. At the same time, when the analgesic effect of alfentanil was presented as a collective response of all patients, the quantal nature of the response was concealed by the wide interindividual variability of the response. Although there was a tendency for larger alfentanil requirements with higher predrug pain intensity, the r coefficient characterizing the relationship ($r = 0.31$) was not statistically significant.[16] Similar results demonstrating only relatively weak relationship ($r = 0.27$, $P < 0.05$) between pain scores and total amount of opioids administered to relieve pain were reported by Taenzer.[17] The quantal nature of within-patient alfentanil dose-analgesic response correlates well with the report by Austin et al.[18] describing a very steep intrapatient meperidine blood concentration-analgesic response curve. With the steep dose-response curve, it is difficult to express pain intensity in terms of analgesic blood concentration because the within-patient difference between opioid concentration that is still ineffective, and the concentration that provides complete analgesia may be too small to detect correct fractions of the response. Figure 2 presents another example: it is impossible to distinguish between the doses of alfentanil providing 50%, 80%, or complete pain relief in an individual patient. An additional indication of weak relationship between pain intensity and opioid requirements is the fact that intrapatient opioid blood concentration values remained relatively constant for 32 to 48 h after surgery despite rapidly declining pain intensity.[19] Thus, a lesser degree of pain did not result in a detectable decrease in the opioid blood concentration required for pain relief.

The role of pain intensity in opioid consumption is obscured by a profound interindividual variability in the sensitivity to opioids. Interpatient variations determined in patients using PCA systems ranged from 3 to 8-fold; at the same time, intrapatient variability was very small.[19–23] In a more recent study,[16] the wide variability in individual sensitivity to opioids was reflected by alfentanil requirements for 50% pain relief ranging from 3 to 18 μg/kg, a sixfold difference. Interpatient variability in sensitivity to opioids mostly depends on the innate responsiveness of the opioid receptor-effector systems and only to a limited degree on pain intensity. However, the level of pain intensity begins to play a very important role in opioid consumption when the pain reaches its low level, the level at which the patient can easily tolerate pain and prefers not to administer an opioid. In this case, PCA usage reflects and could measure not so much the difference between strong and moderate pain, but the difference in the duration of time intervals when the opioid is not needed. A tolerable level of pain when PCA is not in use varies from individual to individual. This is another factor that explains why the correlation between pain intensity and opioid consumption is weak.

Interference of Nonanalgesic Effects of Opioids

Although opioids are used in PCA for their pain-relieving properties, they produce a host of other effects that can influence PCA use by the patients. The antianxiety and mood alteration properties of opioids may contribute to the patient's desire to use a PCA device more frequently. In fact, Taenzer[17] reported that opioid postoperative requirements have better correlation with postoperative anxiety than with pain intensity. A significant correlation between postoperative mood and hourly analgesic use was found by Jamison et al.,[24] although, in the same study, the dose/demand ratios and hourly analgesic use were unrelated to the pain ratings. Although large amounts of opioids may contribute to postoperative depression, it is also possible that patients use PCA not only for its analgesic properties, but also to reduce anxiety and improve their mood. With such patients the PCA usage may not be indicative of the analgesic effect of a drug under investigation. Some drugs with various psychotropic effects may influence PCA dosing not because of their analgesic effects.

Almost unavoidable adverse effects of opioids are another very important factor influencing opioid consumption. Often, patients titrate opioids administered via PCA not to attain a maximal degree of pain relief, but rather to achieve a satisfactory balance between acceptable intensity of pain and adverse effects (i.e., nausea, pruritus, and disorientation). Even when side effects are not reported, patients often do not use PCA to obtain complete pain relief.

Role of Acute Tolerance to the Analgesic Effect of Opioids

Almost all studies using PCA analgesimetry had as an exclusion criterion a history of opioid abuse. Many of them used more strict exclusion criteria related to the use of opioids, such as "chronic opioid use" and/or "daily use of opioids for more than 1 wk." These exclusion criteria were used to eliminate the effect of previously developed tolerance on opioid consumption. Presently, there are clear indications that tolerance to opioids can develop even during the study. It was found that tolerance to remifentanil could develop very rapidly, within several hours.[25] It was also reported that intraoperative use of fentanyl or remifentanil in large doses results in increased postoperative opioid consumption determined by PCA.[26,27] Similar results were observed when large doses of opioids were used during the initial postoperative period: increased morphine administration for 24 h starting immediately after surgery had led to larger opioid requirements during the subsequent 24 h.[28] The differences among various opioids in the development of acute tolerance has long been a matter of controversy.[29,30] Development of acute tolerance due to high doses of opioids used during surgery or

due to a high PCA demand dose or especially to PCA basal opioid infusions can significantly change the outcome of PCA analgesimetry.

Problems of the Patient's Training

Learning how to use PCA has two sides. One is how to operate a PCA device and the other how to cope with postoperative pain by self-administering an opioid. Stress of surgery and postoperative pain make the process of learning very difficult. The easy part of this process, operating the device, can be taught before surgery. However, the most important part of the learning related to pain self-relief cannot be taught in advance. In some patients, the learning process is too prolonged and therefore occupies the part of postoperative time that is most important for obtaining correct values. There is actually no reliable way to control how well patients are managing their pain. If patients receiving PCA correctly maintain their effective blood concentration, the undisclosed increase in a demand dose should lead to the appropriate decrease in demand rate; however, this assumption has not been confirmed.[29] The problems related to the patient's training may negatively affect the assay precision.

Interaction Between Main Outcome Measures

Patients in PCA analgesimetry studies usually have equal degrees of pain relief in the study groups (new drug group vs placebo group). As a result, the difference between the groups in opioid consumption becomes the main measure of the analgesic effect of a new drug. However, the absence of significant differences in pain scores between the groups is not typical for all studies. Table 1 indicates that in five of nine studies there were significant differences between the study groups in both opioid consumption and pain intensity. This happens because not all patients "titrate" pain to a complete relief of spontaneous pain.

The reasons for this are multiple. As indicated above, both insufficient patient training and the patient's desire to avoid unpleasant side effects play a role in opioid self-administration. The other reason is much more complicated and was described by Owen et al.[31] The authors studied the efficacy of a range of demand doses (from 0.5 to 2.0 mg) of morphine for PCA. The patient who received the small dose and had insufficient pain control could have made a demand every 5 min (i.e., 12 per h), but made only a mean of four demands per hour. The authors concluded that there may be a self-imposed maximum demand rate that patients are reluctant to exceed, irrespective of demand dose. A similar observation was made with the addition to PCA of a basal opioid infusion. The co-administration of fixed-rate opioid infusion (when a background infusion would contribute to the blood concentration) should decrease the demand rate proportionally. However, this has not been observed.[32,33]

If the administration of opioids is kept at the same level in all study groups, the effect of an analgesic under investigation expresses itself only by a change in pain intensity. With the use of PCA, a change in opioid consumption is the main index of analgesia, but changes in pain intensity may also be in play. The balance of simultaneous changes in pain intensity and in analgesic consumption represent a difficulty for providing statistically significant results. In most studies, changes in one outcome measure counterbalance changes in another. As a result, changes of both measures often fail to reach a statistically significant level. In addition, with different types of postoperative pain (e.g., orthopedic versus abdominal) changes in opioids consumption may counterbalance changes in pain intensity to a different degree.

Sample Size and Negative Outcome Problems

The required sample size is usually determined on the basis of the magnitude of the expected effect, the variability of the analyzed variable, and the desired probability (power) of observing that effect (with a defined significance level). A power of 80% is usually chosen as adequate. The sample size of different PCA studies varies from 10[13] to 60 and more,[34] which indicate that variability in changes of opioid consumption can be very profound depending on the study circumstances. However, the increase in the size of study groups cannot be the universal answer to all study problems.

Some studies do not find a significant difference between the treatment and placebo groups. If such studies do not have a positive control group in addition to the placebo group, the negative outcome may be explained not only by the absence of analgesic effect but also by insufficient sensitivity of the specific analgesic assay. To prevent such a possibility, an appropriate positive control group should be considered. For example, if one plans a study with a new NSAID, the study groups could include placebo, the new NSAID, and also ketorolac as a positive control. Approximately 1/4-1/5 of the published PCA analgesimetry studies are negative studies without a positive control. The conclusions of these studies may be very problematic.

CONCLUSION

The efficacy of analgesic interventions is judged by the change they induce in the patient's report of pain expressed via various analog scales.[35] With PCA analgesimetry the analgesic demand is a measure of pain. This is an indirect but clinically relevant approach. This approach has multiple problems which are listed in this article.

Most of the PCA analgesimetry problems equally affect both treatment and control groups. Therefore, they can be offset by an increase in the size of the study groups. However, such a solution is not always effective. In the case of a drug with anxiolytic action, a decrease in the opioid demand in the treatment group may be because of the nonanalgesic effect at a time when in the control group the demand is not decreased. In such a case, both groups will not be equally

affected, even if the drug under evaluation does not have any analgesic effect. A similar situation can be with the assessment of a drug with side effects that make worse or, on the contrary, alleviate some of the effects of an opioid used for PCA analgesimetry (i.e., nausea, pruritus, disorientation, acute tolerance). As a result of these effects, the treatment group may not be affected similarly to the placebo group.

The sample size calculation has its own problem when a fixed sample size approach is used. This problem is associated with expected variability in sample size calculation. The expected degree of variability is supposed to reflect conditions typical for the particular study site. The information based on similar studies performed in various sites (with the size of a study group varying from 10 to 60 patients) cannot always be reliable in this regard. The other, more important problem is a negative outcome without a positive control group. To prevent the uncertainty associated with this situation the treatment group should be compared not only with a placebo group, but also with a positive control group. That can exclude the possibility that the assay lacks the sensitivity to measure a difference that is actually present.

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