Anesthesiology
76:510–512, 1992

Subhypnotic Doses of Propofol Relieve Pruritus Induced by Epidural and Intrathecal Morphine

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We investigated the efficacy of subhypnotic doses of propofol for spinal morphine–induced pruritus in a prospective, randomized, double-blind, placebo-controlled study. Fifty patients, ASA physical status 1–3, with spinal morphine–induced pruritus were allocated to receive either 1 ml propofol (10 mg) or 1 ml placebo (Intralipid) intravenously after gynecologic, orthopedic, thoracic, or gastrointestinal surgery. In the absence of a positive response, a second drug treatment was given 5 min later. The persistence of pruritus 5 min after the second treatment dose was considered a treatment failure. All failures then received, in an open fashion, a supplementary dose of propofol (10 mg) and were reevaluated 5 min later. Both groups were well matched. The success rate was significantly greater in the propofol group (84%) than in the placebo (16%) group ($P < 0.05$). Ninety percent of the treatment failures in the placebo group were successfully treated by a supplementary dose of 10 mg propofol. Eight percent of the patients (4% in each group) were resistant to all treatments, including naloxone 0.08 mg intravenously. Three patients had a slight increase in sedation in the propofol group *versus* none in control (not significant). The beneficial effect of treatment was longer than 60 min in 85% of patients in the propofol group and in 100% of the controls (not significant). These results suggest that propofol in a subhypnotic dose is an efficient drug treatment for spinal morphine–induced pruritus. At the dose administered (10 mg), side effects were rare and minor. (Key words: Analgesics, epidural: morphine. Anesthetics, intravenous: propofol. Anesthetic techniques: epidural; intrathecal. Complications: pruritus.)

EPIDURAL OR INTRATHECAL OPIOIDS are used with increasing frequency to achieve postoperative analgesia.[1] Epidural or intrathecal morphine produces an excellent quality of postoperative analgesia. Unfortunately, the incidence of pruritus is high following this mode of administration, especially in patients after cesarean section.[2] Pruritus is unpleasant and often distressing[1] and responds poorly to histamine (H_1) blockers or other conventional treatments.[3] Naloxone is the only drug currently available that effectively treats morphine-induced pruritus.[4] In certain cases, a tendency toward poorer quality of analgesia has been described after naloxone. In an open pilot study,[5] we were able successfully to treat morphine-induced pruritus with propofol. We therefore undertook a prospective, randomized, double-blind, placebo-controlled study to investigate the possible antipruritic properties of propofol in patients who had received epidural or intrathecal morphine.

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Received from the Department of Anesthesiology, University Hospital of Geneva, Geneva, Switzerland. Accepted for publication November 26, 1991.

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Materials and Methods

We studied 50 ASA physical status 1–3 patients of both sexes between the ages of 20 to 70 yr presenting with severe pruritus induced by epidural or intrathecal morphine after elective gynecologic, gastrointestinal, thoracic, or orthopedic surgery. All patients had a balanced anesthesia including thiopental, vecuronium, isoflurane, and fentanyl. None received intravenous opioids in the postoperative period. Only pruritus appearing within the first 24 h postoperatively was studied. Morphine was administered spinally in all patients at the end of the surgery to provide analgesia.

Patients with a known allergy to propofol, a history of any disease associated with pruritus, or a complaint of pruritus prior to surgery were excluded from the study. All patients gave informed consent prior to inclusion in the study. Institutional and ethical committee approval was obtained. Patients entered the study prospectively. Five patients were excluded because of previous history of skin disease associated with pruritus. Medication was blinded and randomized by our pharmacy, which delivered coded vials of either propofol or Intralipid.

Patients complaining of pruritus were initially described by means of a five-point rating scale (table 1). Patients with a score of 4 or 5 were treated with 1 ml of the treatment drug (propofol 10 mg or placebo) intravenously. Five minutes later, patients were reevaluated using the rating scale. A rating scale score of 1 or 2 was considered a success; patients with a score greater than 2 were given a second milliliter of the treatment drug. Treatment was documented as a definitive failure if, 5 min after the second dose, patients had a score greater than 2. Patients whose treatment had failed then received 1 ml propofol in an open fashion and were reevaluated 5 min later. In the absence of improvement (rating score greater than 2), naloxone 0.08 mg was given intravenously. Patients were assessed every 10 min for 60 min, and the time of the reappearance of pruritus was noted.

Other parameters documented in the course of the study were sedation (four-point rating scale, table 2) and postoperative pain (10-point verbal rating scale). After each drug administration, the presence of pain on injection, dizziness, mood change, hallucinations, and hemodynamic values (heart rate and blood pressure) were noted.

Statistical analysis was carried out using nonparametric methods with the Mann-Whitney and Fisher's exact test.

TABLE 1. Pruritus Rating Scale

1. No (or disappearance of) pruritus.
2. Pruritus without itching and scratching; treatment not necessary.
3. Pruritus with itching; treatment desirable.
4. Severe pruritus and itching; treatment necessary.
5. Intractable pruritus and itching.

Demographic data for the groups were compared using Student's t test. $P < 0.05$ was considered significant.

Results

Both groups were comparable with regard to demographic data, type of surgical procedure, method, and dosage of opioid administration (epidural *vs.* intrathecal) (table 3). In the propofol group, 20 patients received 4 mg epidural morphine (16 in the placebo group), and 2 received 3.2 mg (4 in the placebo group). The intrathecal morphine dose was 400 μg and 300 μg in the propofol group (1 and 2 times, respectively) and in the placebo group (2 and 3 times, respectively).

The treatment success rate was significantly greater in the propofol group (84%) than in the placebo group (16%) ($P < 0.05$). The duration of action of propofol was greater than 1 h in 18 patients, 40 min in 2, and 50 min in 1 patient. All successes in the control group lasted more than 1 h. Among the cases of failed treatment in the propofol group, pruritus improved in 2 patients after the open supplementary dose of propofol. The other 2 patients were unresponsive to supplementary open propofol as well as to naloxone. In the placebo group, 90% of patients were subsequently successfully treated by 1 ml propofol (open arm of the study). The other 2 who did not respond to propofol also were resistant to naloxone. The sedation scale increased by one point (1–2 on the rating scale) in 3 patients in the propofol group and none in the placebo group (not significant). The level of postoperative pain remained unchanged after each drug administration and also during the 60-min study observation in both groups. Pain on injection, changes in mood, and/or hallucinations were not reported in either group. Among the Intralipid treatment failures, dizziness occurred in 2 patients after administration of open propofol. Hemodynamic changes were similar in both groups and were nonsignificant. Neither respiratory rate nor hemoglobin oxygen saturation by pulse oximetry changed in either group.

TABLE 2. Sedation Rating Scale

1. Patient fully awake.
2. Patient somnolent; response to call.
3. Patient somnolent; no response to call; response to verbal stimulation.
4. Patient asleep; response to painful stimulation.

TABLE 3. Characteristics of Patients

	Propofol Group	Placebo Group
n	25	25
Age	48 ± 3	55 ± 4
Sex (M/F)	11/14	12/13
Surgery type (D/G/T/O)	9/9/4/3	9/9/6/1
E/I	22/3	20/5

D = gastrointestinal; G = gynecologic; T = thoracic; O = orthopedic; E = epidural; I = intrathecal.

Discussion

The incidence of pruritus after epidural or intrathecal opioids varies from 0 to 100%.[6,7] This type of pruritus is particularly difficult to manage and is generally resistant to conventional treatment.[3] Our study is the first to investigate the effect of propofol on opiate-induced pruritus.

We were able to demonstrate that the success rate of treatment with propofol was significantly greater than with placebo. This success was achieved without significant hemodynamic changes or side effects. Of the four patients with failed treatment in the propofol group, half remained unresponsive to all further treatment (additional propofol [10 mg intravenously] or naloxone [0.08 mg intravenously]). This is surprising, because naloxone is at present considered the treatment of choice for this type of pruritus.[4] The effect of Intralipid on pruritus has not been studied. However, the very high success rate of open propofol in the Intralipid failure group makes a therapeutic effect of Intralipid on pruritus most unlikely. It is noteworthy that the placebo success rate of 16% with Intralipid is relatively low. Perhaps psychological factors play a lesser role in opioid-induced pruritus than with other symptoms (*e.g.*, nausea and vomiting.)

The duration of antipruritic action in our study was much longer than the normal duration of hypnotic action (5–7 min)[8] achieved with the much larger doses of propofol used for anesthetic induction. In addition, the dose of propofol we used was truly subhypnotic. These factors make hypnosis an unlikely explanation for propofol's beneficial effects in this setting.

Sedation did not significantly increase during the study for the two groups. It has been shown that histamine (H_1) blockers, which possess sedative central nervous system actions, are more effective in treating pruritus, especially if it is associated with the release of histamine.[9] In our study, the efficacy of antipruritic action appeared unrelated to sedation levels, but our study design does not exclude the presence of mild, subclinical sedation.

Pain and itch are frequently described as being closely related.[10] Pain scores after each administration of propofol remained unchanged for all patients in our study. Moreover, the quality or quantity of the analgesia provided by epidural or intrathecal opiates did not change during the

study period. Thus in our study, the effects of propofol on pain and itch seem unrelated.

We chose the dose of 10 mg propofol after performing an open study[5] that demonstrated the efficacy of this dose. Indeed, this dose successfully treated and prevented further pruritus in 85% of patients for more than 1 h. However, the question of dose–response relationships was not addressed in this study. The 5-min interval between propofol doses was chosen because we had observed no further improvement in pruritus 5 min after propofol in our pilot study. A high percentage of successfully treated patients remained itch-free for longer than the empirically chosen observation period (1 h). The mean duration of relief of pruritus was 3–6 h. Additional studies are necessary to determine more precisely the dose–time relationships of propofol treatment for opioid induced pruritus.

The precise etiology of pruritus in this clinical setting remains unknown.[11] Intrathecal or epidural opioids have been shown to be associated with pruritus,[12,13] with morphine consistently demonstrating a higher pruritus rate than other opioids.[14] Larger doses of spinal morphine result in a greater incidence of pruritus.[15] Histamine (H_1) blockers, effective in treating pruritus associated with parenteral morphine,[9] seem ineffective in the therapy of pruritus due to spinal morphine.[3] Partial μ-receptor antagonists are considered effective for the treatment[16] and prophylaxis[17] of spinal morphine–induced pruritus, whereas complete μ-receptor antagonism (with naloxone or naltrexone) is the most successful treatment.[18] However, naloxone therapy has been associated in certain cases with a concomitant reduction in analgesia.[19] The most convincing hypotheses to date postulate that pruritus due to spinal morphine is the result of local, particularly spinal cord, stimulation due to excitatory effects of high morphine concentrations.[10] Morphine has been shown to have a facilitatory action on nonnociceptive neurons in the posterior horn.[20] It is noteworthy that propofol, in contrast to other general anesthetics, has been shown to produce marked spinal depression, in particular of the dorsal and ventral horns.[21] Thus, it would not seem unreasonable to postulate that propofol—in contrast to naloxone, the antipruritic action of which seems to result mainly from a block of central enkephalinergic transmission[11]—exerts its antipruritic action through the inhibition of posterior horn transmission. The exact pathways and mechanisms involved merit further study.

In conclusion, this study demonstrates that propofol in subhypnotic doses is effective in treating spinal morphine–induced pruritus without affecting the quality of analgesia. At the dose used (10 mg propofol), side effects were rare and minor.

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