Preliminary Communication

Adjuvant propofol enables better control of nausea and emesis secondary to chemotherapy for breast cancer

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We investigated the prophylactic antiemetic effect of added low-dose infusion of propofol in patients exhibiting nausea and vomiting refractory to dexamethasone and serotonin antagonist during non-cisplatin chemotherapy for breast cancer. In a prospective open longitudinal study, 117 patients who had more than five episodes of nausea and vomiting in their first chemotherapy cycle during the first 24 hr completed the study. They received in addition to the usual prophylactic antiemetic regimen a continuous intravenous infusion of 1 mg · kg^{-1} · hr^{-1} propofol started four hours before chemotherapy and continued up to 24 hr for the two subsequent cycles. The number of vomiting/nausea episodes, level of sedation, patient activity, appetite and preference for future chemotherapy cycles were assessed. In the propofol supplemented cycles 90 and 80% of patients, during the 1st and 2nd propofol-assisted cycle respectively, were free of nausea and vomiting during the first 24 hr after chemotherapy. Patients were more frequently active and had more appetite during the propofol-assisted cycles. No propofol-associated side effects were observed. We conclude that the addition of a subhypnotic infusion of propofol enables better control of nausea and vomiting caused by non-cisplatin chemotherapy in the first 24 hr post-treatment.

Nous avons évalué l'efficacité antiémétique d'une perfusion à faible concentration de propofol sur des patientes qui présentaient des nausées et vomissements réfractaires à la déxaméthasone et à l'antagoniste de la sérotonine pendant une chimiothérapie sans cisplatine administrée contre le cancer du sein. Cent dix-sept patientes qui avaient présenté plus de cinq épisodes de nausées et vomissements pendant les premières 24 h de leur premier cycle de chimiothérapie ont participé à cette étude prospective longitudinale ouverte. En plus de leur médication antiémétique usuelle, une perfusion de propofol 1 mg · kg^{-1} · h^{-1} a été débutée quatre heures avant la chimiothérapie et continuée pendant 24 h pour deux cycles subséquents. Le nombre d'épisodes de nausées/vomissements, le niveau de sédation, l'activité, l'appétit et la préférence manifestée pour la chimiothérapie à venir sont évalués. Lors des cycles additionnés de propofol, 90 et 80% des patientes n'ont présenté ni nausées ni vomissements au cours des premières 24 h du 1er et 2ième cycles post-chimiothérapie. Les patientes étaient plus actives et avaient plus d'appétit pendant les cycles incluant le propofol. Nous n'avons pas observé d'effets secondaires associés au propofol. Nous concluons que l'ajout de propofol en perfusion à des doses sous-hypnotiques permet un meilleur contrôle des nausées et des vomissements provoqués par une chimiothérapie sans cisplatine au cours des 24 h qui suivent le traitement.

Key words
ANAESTHETICS, INTRAVENOUS: propofol;
COMPLICATIONS: vomiting;
VOMITING: antiemetics, nausea.

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Chemotherapy-associated nausea and vomiting represent one of the most distressing and unpleasant problems of cancer treatment[1] and can cause considerable delayed

psychological morbidity, such as anticipatory nausea and vomiting, depression, and reduced patient compliance. A number of antiemetic drug regimens have been introduced to try to control nausea and vomiting associated with cytotoxic cancer therapies. Selective serotonin antagonists (5HT3-antagonists) have recently been shown to be efficient against nausea and vomiting secondary to cisplatin and non-cisplatin based chemotherapy, with few major side-effects.[2,3] However, a large proportion of patients (10–20%) still experience inadequate control of their chemotherapy-associated nausea and vomiting with one of the most efficient antiemetic regimens available, i.e., serotonin antagonist plus dexamethasone.[4]

Subhypnotic doses of propofol have been demonstrated to possess direct antiemetic properties.[5] Interestingly, propofol also has anxiolytic effects at the same subhypnotic dose range.[6] In children receiving cancer treatment, propofol was shown to improve the control of nausea and vomiting.[7]

The observation of these properties led us to investigate the usefulness of propofol in subhypnotic doses for the management of chemotherapy-associated nausea and emesis unresponsive to selective serotonin antagonists and dexamethasone in patients receiving emetogenic non-cisplatin cytotoxic drugs.

Methods

Patients who suffered during their first chemotherapy cycle from more than five emetic episodes in the first 24 hr despite antiemetic prophylaxis (dexamethasone 10 mg *iv* and ondansetron 2 × 8 mg *iv*) were prospectively included in the study after informed consent was obtained. The patients were investigated in the two subsequent chemotherapy cycles, which remained unchanged in terms of cytotoxic therapy and antiemetic prophylaxis apart from the addition of propofol. Propofol was added as a continuous infusion at 1 $mg \cdot kg^{-1} \cdot hr^{-1}$. The infusion was started four hours before (approx. 2 p.m.) chemotherapy induction (approx. 6 p.m.) and continued for 24 hr.

The variables were documented by the attending nurse at two-hourly intervals starting four hours pre-chemotherapy:

- number of vomiting or retching episodes
- observer sedation rating score (SRS) (0 = wide awake; 1 = slight sleepiness; 2 = asleep, verbally arousable; 3 = asleep, rousable by shaking)
- heart rate and blood pressure.

Results

In the 24 mo period, 20 of 117 patients (17%) met the inclusion criteria. All had breast cancer, the median age was 56 yr (range: 45–72). Seven received CMF (cyclophosphamide 600 $mg \cdot m^{-2}$ + methotrexate 40 mg m^{-2} + 5-fluoro-uracil 600 $mg \cdot m^{-2}$), 13 received EFL (epirubicin 120 $mg \cdot m^{-2}$ + 5-fluorouracil 400 mg m^{-2}) as cytotoxic regimen.

All 20 patients completed the subsequent two chemotherapy cycles (i.e., a total of three cycles). None was excluded due to toxicity or insufficient antiemetic prophylaxis. Adding propofol resulted in control of nausea and vomiting in 90 and 80% during the first 24 hr of both subsequent cycles respectively. No sedation was observed during the propofol cycles, no other side effects were seen. All patients preferred propofol-assisted chemotherapy.

Discussion

The addition of propofol to one of the most efficient anti-emetic regimen in use allowed improved control of nausea and vomiting in previously refractory patients, during the first 24 hr after induction of chemotherapy. These results are bolstered by the fact that the patients studied were a difficult group previously having experienced uncontrolled nausea and vomiting with the usual psychological sequelae this entails.[8]

A parallel double-blind placebo (control) group might be considered lacking in the design of this study. We chose to use a prospective open study design at this stage, with patients acting as their own controls, in view of the novelty in this use of propofol.

The mechanisms of propofol's antiemetic action have not been studied so far. This drug has more uniform depressant action[9] on the central nervous system than other anaesthetic drugs. It might thus be expected to depress severely the brain stem structures involved in the genesis of nausea and vomiting, such as the chemoreceptor trigger zone or the vagal nuclei. No sedation was clinically evident during the study, which again would argue against its involvement in antiemetic actions.

Propofol possesses direct antiemetic properties.[5] Recent experimental study suggests that propofol may act as a non-competitive 5-HT3 antagonist at doses much lower than those needed for anaesthesia.[10] These findings may explain the additional effect of propofol in patients refractory to competitive 5-HT3. Anxiolytic and direct antiemetic effects of propofol make propofol a valuable drug for supportive care in the field of oncology. These potential new indications for the use of propofol are an attractive opening for anaesthetists outside the operating room.

Conclusion

The use of propofol as adjuvant to dexamethasone combined with selective serotonin antagonists for non-cisplatin chemotherapy improves antiemetic control.

These results should be confirmed by double-blind, randomized controlled studies.

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