Pharmacological effects of intravenous melatonin: comparative studies with thiopental and propofol


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Background. Possible utility of high-dose i.v. melatonin as an anaesthetic adjuvant has not been studied. This study compared its effects with thiopental and propofol.

Methods. Sprague Dawley rats were assigned to receive bolus or cumulative i.v. doses of melatonin, thiopental or propofol. Righting reflex, hindpaw withdrawal to a noxious stimulus, response to tail clamping and haemodynamic effects were assessed.

Results. Melatonin caused a dose-dependent increase in paw withdrawal threshold and the percent of rats displaying loss of the righting reflex. Melatonin was comparable to thiopental and propofol in terms of its rapid onset of hypnosis. The mean ED₅₀ values for loss of righting reflex were 5.4 (SEM 1.2), 12.5 (1.1) and 178 (1.1) mg kg⁻¹ for propofol, thiopental and melatonin, respectively. The percent of rats displaying loss of response to tail clamping was greater with propofol than with melatonin (P<0.05). Haemodynamic changes produced by melatonin or propofol were similar in onset and magnitude.

Conclusions. I.V. melatonin can exert hypnotic effects similar to those observed with thiopental and propofol. Melatonin exhibited significant antinociceptive effects but was less effective in abolishing the response to tail clamping.

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Exogenous melatonin, commonly administered orally, produces a number of beneficial actions,¹² including anticonvulsant³ and antinociceptive effects.⁴ The pharmacologic effects of i.v. melatonin, particularly at high doses, have not been reported. These studies were designed to determine whether high-dose i.v. melatonin exhibits properties that would be useful in a general anaesthetic or anaesthetic adjuvant. To this end, the effect of increasing doses of melatonin on righting reflex, responses to noxious stimuli, and haemodynamics were compared with thiopental and propofol.

Methods and results

With institutional approval, non-fasting male Sprague Dawley rats (Harlan, Indianapolis, IN, USA) were weighed and anaesthetized with isoflurane. In all rats, the right jugular vein was cannulated with a heparinized saline-filled catheter. Other rats were prepared for haemodynamic studies, in which the right carotid artery was also cannulated. Studies were carried out 5–7 days after surgery.

The following drugs were used: thiopental (Abbott Laboratories, Abbott Park, IL, USA), propofol emulsion (AstraZeneca Pharmaceuticals, Wilmington, DE, USA), and melatonin (Sigma Chemical Co., St Louis, MO, USA). Thiopental was dissolved in saline. Melatonin was dissolved in a mixture of propylene glycol (Fisher Chemicals, Fair Lawn, NJ, USA) 25% v/v and 1-methyl-2-pyrrolidinone (Aldrich Chemicals, Milwaukee, WI, USA) 25% v/v in sterile water.

The loss of righting reflex and response to paw pinch were used as measures of hypnosis and antinociception,
respectively. For righting reflex, the animal was placed on its back and attempts to resume the prone position within 15 s were noted. The pressure at which the rat withdrew or vocalized after a pinch of one hindpaw was determined as a measure of nociceptive threshold. Pressure was applied across the dorsal and ventral aspects of the paw by placing the paw within the jaws of a sponge-clamp assembly equipped with a subminiature low-profile load cell (Omega, Stamford, CT, USA). Application of a pinch pressure of 60 mm Hg (the cut-off value) evoked a vigorous escape response in awake rats and was judged to be very painful when applied to a fold of the investigator’s skin.

For dose–response studies, unanaesthetized animals received three i.v. doses of thiopental 6.67 mg kg\(^{-1}\), giving a cumulative dose of 20 mg kg\(^{-1}\), three i.v. doses of propofol 3.3 mg kg\(^{-1}\), giving a cumulative dose of 10 mg kg\(^{-1}\), or three i.v. doses of melatonin 70 mg kg\(^{-1}\), giving a cumulative dose of 210 mg kg\(^{-1}\). Other rats received three cumulative doses of either saline, Intralipid™ (propofol vehicle) or the vehicle.
in which melatonin was administered. A dosing interval of about 60 s was used. Each dose was administered in a volume of 0.2 ml and the total volume of drug injected did not exceed 0.6 ml. Measurements of loss of righting reflex and paw withdrawal threshold were made before (baseline) and after drug administration and at fixed intervals in the 20 min that followed administration of the final cumulative dose.

For tail-clamp studies, different groups of rats were assigned to receive a single i.v. bolus of thiopental 20 mg kg$^{-1}$, propofol 10 mg kg$^{-1}$, melatonin 257 mg kg$^{-1}$ or the vehicles in which these drugs were dissolved. Tail clamp was tested by application of a rubber-clad vascular clamp (22 cm DeBakey) across the proximal third of the tail. Purposeful movement of the hind limbs and/or the head was noted as a positive response.

Haemodynamic data were acquired after placing a conscious, unrestrained rat into an open-top chamber. A pressure transducer was attached to the arterial catheter. Equipotent doses of thiopental 23.8 mg kg$^{-1}$, propofol 14.9 mg kg$^{-1}$, melatonin 312 mg kg$^{-1}$ or the vehicles for these drugs were administered via the internal jugular venous catheter. Systolic, mean and diastolic pressures were recorded for 10 min.

Probit analysis using WinNonlin Professional version 3.1 (Pharsight Corporation, Cary, NC, USA) was used to fit dose–response curves and to estimate ED$_{50}$ values. Raw data were transformed to a quantal response to generate dose–response graphs. To obtain a measure of the antinociceptive effects of these drugs, paw withdrawal data were also expressed as mm Hg at which a response occurred.

Tail-clamp and haemodynamic data were analysed using two-way ANOVA with repeated measures. Comparisons between each drug and its vehicle were performed using the Mann–Whitney U test. All statistical analyses were performed using BMDP Dynamic statistical package (University of California Press, Berkeley, CA, USA). Results are expressed as mean (SEM), and were considered significant at $P<0.05$.

Cumulative i.v. injection of thiopental produced a dose-dependent increase in the percent of rats displaying loss of righting reflex, but had no consistent effect on paw withdrawal threshold (Fig. 1A and 1B). Propofol and melatonin caused dose-dependent increases in paw withdrawal threshold, as well as an increase in the percent of rats displaying loss of righting reflex. The mean ED$_{50}$ values for loss of response to paw pressure were 17.7 (SEM 2.7) and 91.3 (1.2) mg kg$^{-1}$ for propofol and melatonin, respectively. Corresponding values for loss of righting reflex for thiopental, propofol and melatonin were 12.5 (1.1), 5.4 (1.2) and 178 (1.1) mg kg$^{-1}$, respectively.

Mean paw withdrawal thresholds following three cumulative doses of thiopental were 19.8 (5.1), 10.6 (1.6) and 12.3 (1.9) mm Hg, respectively. Corresponding values for three cumulative doses of propofol were 15.2 (5.5), 24.8 (10) and 37.7 (9.8) and for melatonin were 32.4 (7.5), 49.3 (7.1) and 60 (0) mm Hg, respectively.

Bolus injection of thiopental 20 mg kg$^{-1}$ resulted in loss of response to tail clamping in 71% of rats at 1 and 2 min ($P<0.05$). Administration of propofol 10 mg kg$^{-1}$ resulted in loss of response to tail clamping in 100% of rats at 1 and 2 min and in 57% of rats at 5 min ($P<0.05$). Bolus injection of melatonin 257 mg kg$^{-1}$ resulted in loss of response to tail clamping in 43% of rats at 2 and 10 min ($P=0.07$). Administration of saline, Intralipid$^{	ext{TM}}$ or the melatonin vehicle did not affect righting reflex, paw withdrawal threshold or tail clamp responses.

A significant reduction in mean arterial pressure occurred following bolus administration of equipotent doses of propofol or melatonin, but not thiopental, when compared with their respective vehicles (Fig. 1C).

**Discussion**

I.V. administration of melatonin induced a profound dose-dependent hypnotic state in rats that was characterized by a rapid loss of righting reflex, and an antinociceptive effect. These properties are desirable in anaesthetic agents or anaesthetic adjuvants. However, melatonin was considerably less potent than either propofol or thiopental when ED$_{50}$ values for loss of righting reflex are compared. A number of behavioural studies have shown that melatonin exerts an antinociceptive action against thermal, chemical and electrical stimuli in rodents.4,5 In this study, thiopental did not increase paw withdrawal threshold. This finding is not unexpected since evidence indicates that thiopental is hyperalgesic, as demonstrated in both human and animal studies.6

In this study, the hypotensive effects of melatonin were comparable to those of propofol. Consistent with our observations, Mulier and colleagues7 noted that the cardiodepressant effects of propofol are more pronounced and more prolonged than those of equipotent doses of thiopental.

This study examined whether melatonin, at doses greater than those that produce somnolence, has properties considered beneficial in anaesthetic adjuvants or in general anaesthetics *per se*. Melatonin was considerably less potent than either propofol or thiopental. Its haemodynamic effects, while comparable with those of an equipotent dose of propofol, did not afford an improvement. Furthermore, melatonin was not effective in abolishing the response to tail clamping. Thus, while melatonin appears to have properties of interest in an anaesthetic adjuvant, it does not itself possess sufficient efficacy to warrant consideration as a general anaesthetic.

A number of melatonin analogues of greater potency and efficacy are currently being studied to determine their effects on the induction of general anaesthesia.
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Effect of continuous low-dose intravenous diltiazem on epidural fentanyl analgesia after lower abdominal surgery

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Background. The postoperative opioid-sparing effects of systemic L-type calcium channel blockers are controversial. We investigated whether the postoperative analgesic effect of epidural fentanyl was enhanced by i.v. infusion of diltiazem at a rate that would minimize any cardiovascular depressant effect.

Methods. After elective lower abdominal gynaecological surgery, 30 patients were randomized to receive continuous i.v. diltiazem 1 mg kg⁻¹ min⁻¹ (diltiazem group) or the same volume of saline (control group) for 24 h. Cumulative postoperative epidural fentanyl consumption, visual analogue scale (VAS) scores and verbal rating scores (VRS) at rest and during mobilization, sedation scores, incidence of side-effects and overall patient satisfaction were assessed.

Results. There was no significant difference in cumulative epidural fentanyl consumption between the groups at any period. Although there were no statistically significant differences in VAS scores, VRS, sedation scores, incidence of side-effects and overall patient satisfaction, there was a trend to an increased incidence of nausea in the diltiazem group.

Conclusions. Continuous i.v. infusion of diltiazem did not reduce epidural fentanyl consumption when administered at dosages having minimal haemodynamic depressant effects.

Keywords: analgesic techniques, epidural; analgesics opioid, fentanyl; heart, antiarrhythmics, diltiazem; heart block, calcium channel blockers; pain, postoperative

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