INTRAOPERATIVE BRADYCARDIA AND HYPOTENSION ASSOCIATED WITH TIMOLOL AND PILOCARPINE EYE DROPS

P. MISHRA, T. N. CALVEY, N. E. WILLIAMS AND G. R. MURRAY

SUMMARY

A 69-yr-old man, who was concurrently being treated with pilocarpine nitrate and timolol maleate eye drops, developed a bradycardia and became hypotensive during halothane anaesthesia. Both timolol and pilocarpine were subsequently identified in a 24-h collection of urine. Timolol (but not pilocarpine) was detected in a sample of plasma removed during surgery; the plasma concentration of timolol (2.6 ng ml$^{-1}$) was consistent with partial $\beta$-adrenoceptor blockade. It is postulated that this action may have been enhanced during halothane anaesthesia with resultant bradycardia and hypotension. Pilocarpine may have had a contributory effect.

When ecolithiopate eye drops are used in the management of glaucoma, they may enhance and prolong the action of suxamethonium (Gesztes, 1966; Pantuck, 1966). Other complications during surgery that are directly and causally related to the use of local ophthalmic preparations are uncommon. We report a case in which the patient, concurrently treated with timolol maleate and pilocarpine nitrate eye drops, developed bradycardia and hypotension during general anaesthesia although the heart rate, both before and after operation, was within normal limits.

CASE REPORT

A 69-yr-old man (body weight 82 kg) who had previously undergone surgical removal of a squamous cell carcinoma of the right heel was admitted for block dissection of enlarged inguinal lymph nodes. During the previous 4 yr, the patient had been treated for glaucoma with both 2% pilocarpine nitrate eye drops (1 drop twice daily to the left eye) and 0.5% timolol maleate eye drops (1 drop four times daily to the right eye). Consequently, the pupils were unequal in size. Treatment was continued after admission to hospital.

Nitrazepam 10 mg was given on the night before surgery and diazepam 10 mg in divided doses on the day of surgery. Immediately before the induction of anaesthesia, heart rate was 72 beat min$^{-1}$, arterial pressure was 180/110 mm Hg, and the ECG was within normal limits. Hypertensive changes were not present in the retina or in other target organs. Anaesthesia was induced with thiopentone 350 mg and, following the injection of atracurium 0.6 mg kg$^{-1}$, the trachea was intubated and anaesthesia was maintained with 0.5% halothane and 70% nitrous oxide in oxygen. Ventilation was controlled. Within 10 min, the heart rate had decreased to 50 beat min$^{-1}$; arterial pressure was 100/60 mm Hg. Atropine sulphate 0.3 mg was given with no effect; at 15 min, the arterial pressure had decreased to 70/40 mm Hg, heart rate was 40 beat min$^{-1}$, and an A-V nodal rhythm was present on the ECG. Halothane was discontinued for 5 min; during this time the arterial pressure did not change, although the heart rate increased slightly (to 45 beat min$^{-1}$). At 20 min, further atropine 0.3 mg was given, but there was no change in heart rate or arterial pressure. During the remaining 120 min of surgery, arterial pressure remained at 70/40 mm Hg, and the heart rate ranged between 39 and 44 beat min$^{-1}$. During the operation, supplementary doses of atracurium were given (0.3 mg kg$^{-1}$ at 75 min, and 0.2 mg kg$^{-1}$ at 130 min), with no effect on heart rate or arterial pressure. After 150 min, halothane was discontinued and residual neuromuscular blockade antagonized with neostigmine 2.5 mg and atropine 0.6 mg. At 180 min, the arterial pressure had increased to 130/90 mm Hg, and the heart rate was 65 beat min$^{-1}$. There was no significant fluid loss or replacement during surgery, and recovery from anaesthesia was uneventful.


Correspondence to T. N. C., University of Liverpool.
Samples of blood were removed during surgery; a 24-h collection of urine was obtained in the period after operation. During this time, the patient received his usual treatment with timolol and pilocarpine. The concentration of the two drugs in plasma and urine was subsequently measured by gas–liquid chromatography. Pilocarpine was not detected in plasma (sensitivity limit 2 ng ml⁻¹); the total amount of pilocarpine eliminated unchanged in urine in 24 h was 458 µg (11.4% of the dose). Timolol was detected in the sample of plasma obtained during surgery and in the subsequent 24-h collection of urine. During operation, the plasma concentration of timolol was 2.6 ng ml⁻¹; the total amount of the drug eliminated unchanged in urine was 43.3 µg (7.2% of the dose).

DISCUSSION

This patient, who was treated with timolol and pilocarpine throughout the perioperative period, developed a bradycardia and became hypotensive during general anaesthesia. These phenomena could have resulted from other intraoperative factors such as abnormalities in cardiac conduction or excessive sensitivity to halothane anaesthesia, although the other drugs used during surgery are unlikely to be responsible for bradycardia or hypotension. Atracurium has little or no effect on the cardiovascular system (Hughes and Chappie, 1981; Payne and Hughes, 1981). In this patient, the cardiovascular complications did not bear any temporal relationship to its administration. The decrease in arterial pressure may have been related to moderate untreated hypertension; in these conditions, hypotension during operation is not uncommon (Hickler and Vandam, 1970; Prys-Roberts, Meloche and Foëx, 1971, Prys-Roberts et al., 1971).

Nevertheless, there is a degree of circumstantial evidence that the use of the ophthalmic preparations may have played an important role in precipitating these events. In this patient, the plasma concentration of timolol during surgery was 2.6 ng ml⁻¹, and concentrations in this range are generally associated with significant effects on cardiovascular function. Significant haemodynamic effects are known to be produced by systemic β-blockade during general anaesthesia (Johnstone, 1970). Under these conditions, there is a decrease in both heart rate and arterial pressure, and cardiac output may decrease by 25–40% (Stephen, Davie and Scott, 1971). It seems highly probable that the bradycardia and hypotension observed in this patient were precipitated by partial blockade of cardiac β-adrenoceptors during halothane anaesthesia.

The possible role of pilocarpine is more difficult to assess. This long-standing and widely-used mydriatic agent is not known to cause systemic effects following ocular administration, nor has it been implicated in cardiovascular dysfunction associated with anaesthesia. However, in this patient trace amounts of pilocarpine (458 µg) were identified in urine during the period after operation. This represented 11.4% of the dose administered (or possibly a considerably greater proportion of the dose available for absorption, if there was significant overflow or removal by tears). It is thus feasible that systemic pilocarpine may have produced a primary or a supra-additive effect in this patient by its agonist effect on cardiac muscarinic receptors.

The bradycardia and hypotension remained refractory to atropine 0.3 mg, administered on two separate occasions. Possible explanations for this may include (a) the relatively small dose of atropine used; (b) the diminished response to atropine in the presence of significant β-adrenoceptor blockade; and (c) the failure of atropine to displace pilocarpine from muscarinic receptors. Complete S–A blockade may be dependent on the use of relatively large doses of atropine, for example 25–40 µg kg⁻¹ (Chamberlain, Turner and Sneddon, 1967). Doses of this magnitude may have been required to increase the heart rate significantly in this patient.

ACKNOWLEDGEMENTS

It is a pleasure to acknowledge the help and co-operation of Mr D. O. Maisels, and his permission to report this case. Timolol maleate was supplied by Merck, Sharp & Dohme Limited.

REFERENCES


---

**RESUME**

Un homme de 69 ans, qui était traité par ailleurs avec des gouttes oculaires de maleate de timolol et de nitrate de pilocarpine, a présenté une bradycardie puis une hypotension au cours d’une anesthésie à l’halothane. Le timolol et la pilocarpine ont pu ensuite être tous deux identifiés dans un recueil des urines des 24 h. Le timolol, mais pas la pilocarpine, a été détecté dans un échantillon de plasma prélevé au cours de l’intervention; la concentration plasmatique de timolol (2,6 ng ml⁻¹) était compatible avec un blocage partiel des récepteurs beta-adrénergiques. Nous postulons que cette action ait pu être aggravée au cours de l’anesthésie à l’halothane, avec en conséquence une bradycardie et une hypotension. La pilocarpine a pu avoir une effet additionnel.

---

**SUMARIO**

Un paciente de 69 años de edad, al que se le suministraron gotas de timolol y de nitrato de pilocarpina, simultáneamente, desarrolló una bradicardia e hipotensión durante la anestesia con halotano. Tanto el timolol como la pilocarpina fueron identificados posteriormente en una colección de urina correspondiente a un periodo de 24 horas. Se detectó timolol (pero no pilocarpina) en una muestra de plasma obtenida durante intervención quirúrgica; la concentración de timolol en el plasma (2,6 ng ml⁻¹) fue consistente con el bloqueo β-adrenoceptor parcial. Se postula que esto podría haberse reforzado durante la anestesia con halotano, produciéndose hipotensión y bradicardia. La pilocarpina puede haber contribuido al hecho.