EFFECTS OF PROPRANOLOL ON THE ACTION OF NEUROMUSCULAR BLOCKING DRUGS

BY

L. WISLICKI AND I. ROSENBLUM*

Department of Pharmacology, Hebrew University—Hadassah Medical School, Jerusalem, Israel

SUMMARY

The neuromuscular block induced in cats by depolarizing drugs was intensified and the effect of tubocurarine was reduced by intravenous infusions of propranolol, although by themselves they did not affect contraction of skeletal muscle.

The use of propranolol in the treatment of arrhythmias during anaesthesia has recently been discussed by Vickers (1966). After intra-arterial injection of comparatively large doses, propranolol, like the structurally related pronethalol (Tüürker and Kiran, 1965), augments the action of neuromuscular blocking agents (Wislicki and Rosenblum, 1967). It has been shown that propranolol not only blocks adrenergic beta-receptors but that it also has a sympathomimetic effect, apparently by inducing a release of catecholamines from the adrenal medulla (Kayaalp and Kiran, 1966). Since, under different conditions, sympathomimetic amines may antagonize or intensify the action of curarizing drugs (Bowman and Raper, 1966) we investigated whether smaller amounts of propranolol can modify the action of neuromuscular blocking substances.

METHODS

Cats were anaesthetized with chloralose 40 mg/kg and urethane 1 g/kg, given intravenously after ether induction. The tendons of the right tibialis anterior and soleus muscles were cut at their insertions and attached to semi-isometric transducers. The ipsilateral sciatic nerve was sectioned near the sciatic notch and mounted on shielded silver electrodes. The leg was secured in a rigid frame and the muscles were placed under a tension of approximately 200 g. The nerve was stimulated by supramaximal square shocks at the rate of 6/min.

Carotid blood pressure was measured by means of a pressure transducer attached to a cannula and the heart rate was determined from the pulsations of the blood pressure. Respiration was recorded by a transducer connected to one arm of the tracheal cannula. All recordings were made with a multichannel polygraph (E. & M. Instrument Co.).

Propranolol was administered by intravenous infusion; though doses differed in various experiments, the volume of the infusions was kept at 2 ml/hr, by adjusting the concentration of the drug.

Drugs. Suxamethonium chloride (3 cats), decamethonium iodide (3), tubocurarine chloride (3), gallamine triethiodide (4) and propranolol hydrochloride were dissolved in 0.9 per cent NaCl; doses are stated in terms of these salts.

RESULTS

The twitch height of indirectly stimulated skeletal muscles was not diminished by intravenous infusions of propranolol in concentrations of up to 60 μg/kg/min (11 cats). To test for any interaction between propranolol and curarizing drugs the infusion was started 45–60 min after a test dose of a neuromuscular blocking compound had been given. The dosage of propranolol was 10, 20, 60 (4 cats each) and 40 (1 cat) μg/kg/min. When the effect of propranolol was marked as judged by the bradycardia it produced, the same blocking drug as before was injected again while the infusion continued and the blockade was compared with that obtained before the infusion.
Augmentation of decamethonium blockade by infusion of propranolol. Upper tracing is of respiration. Numbers above the blood pressure tracing denote heart rate in beats/min.

With decamethonium such treatment with propranolol increased the depth and duration of the neuromuscular block. From the number of experiments done a dose-response relationship between propranolol dose and depression of neuromuscular transmission could not be established but in the representative case shown in figure 1 a total amount of propranolol of 350 \( \mu \text{g/kg} \) given in 35 minutes converted a partial decamethonium block in the anterior tibialis into a complete block and markedly reduced neuromuscular transmission in the soleus muscle. Similar results were obtained with suxamethonium, the brief action of which allowed us to test in the same animal the influence of prolonged propranolol infusions. Such an experiment (fig. 2) indicated that the intensification and prolongation of the suxamethonium block by propranolol were not greater after infusion lasting 2 hours than they had already been after 45 minutes.
Conversely, intravenous administration of propranolol reduced the neuromuscular block caused by tubocurarine. In spite of this, respiration became depressed and blood pressure declined after the second tubocurarine injection in some cases (e.g. fig. 3) necessitating artificial respiration. Decreases of pulse rate (±SD) were: for 10 μg/kg/min, 5 (± 8) beats/min; for 20 μg/kg/min, 20 (± 1); and for 60 μg/kg/min, 29 (± 7) beats/min. Systemic blood pressure levels during the infusions varied slightly above and below the initial levels.

**DISCUSSION**

The changes in the effect of neuromuscular blocking agents seen after intravenous infusions of propranolol differ not only quantitatively but also qualitatively from the intensification of the action of both depolarizing and non-depolarizing blocking drugs observed after intra-arterial injection of greater amounts of propranolol. The effect of these appears to be related to its local anaesthetic action (Wislicki and Rosenblum, 1967) and is similar to the depression of contraction of skeletal muscle caused by quinidine (Wislicki, 1960). In contrast, the action of intravenous administration of smaller doses of propranolol may be due to its ability to release catecholamines (Kayaalp and Kiran, 1966) which in turn augment the release of acetylcholine (Krnjevic and Miledi, 1958) as indicated by acceleration by adrenaline of the discharge of miniature potentials and by the adrenaline-induced increase in the amplitude of endplate potentials in curarized rat muscle. Since the muscle response to depolarizing drugs resembles that to acetylcholine (Paton, 1951), an increased release of the latter at the neuromuscular junction after intravenous administration of propranolol would result, by a synergistic action, in an intensification of the neuromuscular blocking effect of decamethonium and suxamethonium. Likewise, it would produce an anti-curare effect, as has been repeatedly observed in frogs (Hutter and Loewenstein, 1955) and mammals (see Bowman, Goldberg and Raper, 1962).

Catecholamines in large doses act by stabilizing the muscle membrane and by decreasing its electrical excitability (Krnjevic and Miledi, 1958). Such an action could account, in the presence of an increased sensitivity, for the intensification of the gallamine block occasionally observed after prolonged administration of propranolol in the same manner that it may be responsible for the potentiation by adrenaline of the tubocurarine block seen in rabbits (Naess and Sirens, 1953).
REFERENCES


LES EFFETS DE PROPAHOLOL SUR L’ACTION DES BLOQUEURS NEUROMUSCULAIRES

SOMMAIRE
Le block neuromusculaire produit chez le chat par des médicaments dépolarisants fut intensifié et l’effet de tubocurarine réduit par l’infusion intraveineuse de propranolol, en dépit du fait que d’eux-mêmes ils n’exercaient pas d’effet sur la contraction des muscles squelettiques.

EINFLUSSE VON PROPAHOLOL AUF DIE WIRKUNG NEUROMUSKULAR BLOCKIERENDER SUBSTANZEN

ZUSAMMENFASSUNG
Durch intravenöse Infusion von Propanolol wurde die bei Katzen mit depolarisierenden Substanzen ausgelöste neuromuskuläre Blockade verstärkt und die Wirkung von Tubocurarin herabgesetzt, obwohl dieses von sich aus die Kontraktion des Skelettmuskels nicht beeinflußte.

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