EXPERIMENTAL STUDIES WITH PROPRANOLOL AS A LOCAL ANAESTHETIC

by

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SUMMARY

The local anaesthetic activity of propranolol has been studied on the frog lumbar plexus and dog spinal cord. The anaesthetic action was of short latency and fairly long duration. The local toxicological studies after repeated local administration of propranolol did not reveal any sign of acute irritation or delayed tissue damage on rabbit cornea, guinea-pig skin and dog spinal cord. As judged by formalin-induced arthritis studies in rats, propranolol possesses anti-inflammatory activity.

Propranolol, a beta-receptor blocking agent, possesses strong local anaesthetic activity (Morales-Aguilera and Vaughan Williams, 1965; Jaju, Sinha and Srimal, 1966). As a surface anaesthetic it is two and a half times more potent than cocaine and as an infiltration anaesthetic it is five times more potent than procaine (Jaju, Sinha, Srimal, 1966). Recently propranolol has been used with success as a local anaesthetic in minor surgical procedures, e.g. lacerated injuries, ear, nose and throat operations (Sinha et al., 1967; Dhasmana et al., 1967), eye operations (Singh et al., 1969) and in dental surgery (Mathur et al., 1968). However, no report is available regarding the efficacy of propranolol as a spinal anaesthetic or its potency in blocking nerve plexuses (plexus anaesthesia). Encouraging results obtained in preliminary clinical trials prompted further investigation of the pharmacological and toxicological aspects of propranolol as a local anaesthetic.

The purpose of the present study was to investigate the potency of propranolol as a spinal and plexus anaesthetic and to investigate the acute and chronic local toxicities of propranolol on the skin, cornea and spinal cord.

METHODS

Plexus and spinal anaesthetic studies.

The plexus anaesthetic studies were carried out in thirty frogs according to the method of Bulbring and Wajda (1945). A cotton swab soaked in 0.2 ml of the solution of the anaesthetic agent was applied to the surface of the exposed lumbar plexus of acutely decapitated frogs with the upper spinal cord destroyed. The time taken to abolish the reflex contraction to sensory stimulus (dipping the leg in dilute hydrochloric acid) was recorded. Each concentration of propranolol and cocaine was tested in a group of five frogs.

The spinal anaesthetic effect of different concentrations (0.5–2.0 per cent) of propranolol (2.0 ml) injected intrathecally at the level of L₁–L₂ was observed in six dogs. Observations of the motor power and sensory perception to pinprick were carried out every 15 minutes for a period of 4 hours.

Histological studies.

The effect of the cornea was studied after instillation of 5 drops of 2.0 per cent propranolol solution every 5 minutes for a period of half an hour daily for 3 days in six rabbits. On the 4th day the cornea was removed under pentobarbitone anaesthesia (35 mg/kg i.p.). The cornea of the other eye served as a control. The cornea was histologically examined for the presence of inflammatory reaction and tissue damage. Similarly in six guineapigs different concentrations (0.5–2.0 per cent) of propranolol (0.25 ml) were injected intradermally under aseptic conditions in a localized area of one quadrant on the back of each guineapig for 7 consecutive days. Each concentration was injected in six different quadrants. On the 8th day the area of skin was

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removed under pentobarbitone anaesthesia (35 mg/kg i.p.) and histologically examined. The lumbar segments of the spinal cords of the three dogs receiving intrathecal injection of propranolol (2 ml of 2 per cent solution, sp.gr. 1.012) for 3 days were removed under pentobarbitone anaesthesia (30 mg/kg i.v.) and histologically examined. Haematoxylin-eosin stain was employed for staining the tissues.

**Formaldehyde-induced arthritis studies.**

The anti-inflammatory effect of different doses of propranolol (0.1–2.5 mg/100 g) was studied in twenty-four albino rats, according to the method of Brownlee (1950). Rats weighing 100–110 g were divided into groups of six. The anteroposterior diameters of the ankle joints were measured daily for 7 days and 0.1 ml of 2 per cent (v/v) formaldehyde solution was injected subcutaneously under the plantar aponeurosis in each foot on the 1st and 3rd days. One group of six rats served as control. The 7-day average diameter for each group was calculated and the results statistically analyzed.

**RESULTS**

**Local anaesthetic studies.**

**Plexus anaesthesia.** It is evident (fig. 1) that the onset of plexus anaesthetic action of propranolol as judged by abolition of the reflex contraction to sensory stimulus, was slower than that of cocaine. Recovery with propranolol was not observed even after 30 min.

**Spinal anaesthesia.** Intrathecal administration of propranolol (2 ml of 2 per cent solution) produced immediate loss of response to pinprick followed by paralysis of the hind legs. However, concentrations lower than 2.0 per cent produced only muscle weakness lasting from 1 to 2 hours. Muscular twitchings preceding the paralysis were never observed. Partial recovery (both sensory and motor) was observed after 2 hours. Complete recovery was only observed after 4 hours.

**Histological studies.**

After repeated local administration of propranolol no sign of inflammatory reaction or tissue damage was observed in the three test tissues.

**Formaldehyde-induced arthritis studies.**

It is apparent (table I) that propranolol possesses anti-inflammatory property. The anti-inflammatory effect observed with 0.5 and 2.5 mg/100 g of propranolol was found to be significant (P<0.001)

| Table I |
|-----------------|-----------------|-----------------|----------------|
| **Effect of propranolol on formalin-induced arthritis.** | | | |
| | **Dose** | **Average initial ankle diameter (mm ± SE)** | **Average ankle diameter of treated rats during 6-day period (mm ± SE)** | **P** |
| | (mg/100 g) | | | |
| Control | – | 6.92 ± 0.30 | 7.50 ± 0.08 | – |
| Propranolol | 0.1 | 6.83 ± 0.07 | 7.39 ± 0.01 | 0.3 |
| Propranolol | 0.5 | 6.91 ± 0.02 | 6.92 ± 0.04 | <0.001 |
| Propranolol | 2.5 | 6.92 ± 0.12 | 6.93 ± 0.11 | <0.001 |

* Compared with control average 6-day diameter.
DISCUSSION
In the present investigation propranolol has been found to possess a potent anaesthetic action both on the lumbar plexus in the frog and the spinal cord of the dog. Prior to its clinical use as a local anaesthetic due consideration must be given to the local undesirable action of propranolol on tissues which might be the seat(s) of its clinical application as a local anaesthetic. It was observed that propranolol causes neither immediate irritation of tissue, as shown by absence of conjunctival congestion after topical application and muscular twitching after intrathecal administration, nor does it produce any tissue infiltration and/or cytological changes after repeated administration. It was interesting to note that propranolol was observed to possess an anti-inflammatory effect.

ACKNOWLEDGEMENT
The authors are grateful to the Indian Council of Medical Research, New Delhi, for financial assistance and to Imperial Chemical Industries, England, for the gift of propranolol (Inderal).

REFERENCES

ETUDES EXPERIMENTALES AVEC LE PROPRANOLOL COMME ANESTHESIQUE LOCAL

SOMMAIRE
L'activité anesthésique locale du propanolol a été étudiée sur le plexus lombaire de la grenouille et la moelle épinière du chien. Le temps de latence de l'effet anesthésique est court et sa durée assez longue. Les essais toxicologiques locaux après administration locale répétée du propanolol n'ont révélé aucun signe d'irritation aiguë ou de lésions tissulaires retardées au niveau de la cornée du lapin, de la peau du cobaye et de la moelle épinière du chien. L'étude d'arthrites causées par formaldéhyde chez le rat prouve que le propanolol possède une activité anti-inflammatoire.

EXPERIMENTELLE STUDIEN MIT PROPRANOLOL ALS LOKALANÄSTHETIKUM

ZUSAMMENFASSUNG