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The effect of thymoxamine on peripheral blood vessels as monitored by the ^{133}Xe clearance technique

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The rate of clearance of intra-articularly administred ^{133}Xe provides an indirect method for the measurement of synovial tissue perfusion. The effect of an intra-articular injection of thymoxamine, and of isoprenaline was to increase the clearance rate whereas the converse was seen with noradrenaline. The prior administration of thymoxamine did not affect the isoprenaline response. In suitable doses, thymoxamine both prevented, and reversed the noradrenaline effect.

The specific α-adrenergic blocking agent, thymoxamine which acts reversibly by competitive inhibition (Birmingham & Szolcsányi, 1965; Birmingham, Ernest & Newcombe, 1969), affords the opportunity of selectively studying α-receptor function. We have used this compound to examine adrenergic control of the peripheral blood vessels in canine synovium using a radio-isotope technique.

The clearance rate of radioactive xenon (^{133}Xe) from the diarthrodial joint cavity has been shown to be reproducible (Dick, Whaley & others, 1970a), and to provide an indirect measure of synovial tissue perfusion (Dick, St. Onge & others, 1970b).

In the present work the rate of clearance of intra-articularly injected ^{133}Xe from the canine stifle joint was used to monitor the effects of the active compounds on synovial perfusion. The effect of thymoxamine alone was studied, and, to further characterize the result, the effects of isoprenaline and noradrenaline alone and in combination with thymoxamine were examined.

MATERIALS AND METHODS

Both stifle joints of adult greyhounds, 20 to 28 kg, were examined. Anaesthesia was induced with sodium thiopentone (20 mg/kg) and maintained with a 5:3 mixture of nitrous oxide and oxygen and additional (1%) trilene. A catheter in the brachial artery permitted continuous recording of blood pressure and pulse rate.

Injection technique

A 15/16 gauge needle was inserted into the joint cavity by a medial infra-patellar approach and its position confirmed by aspiration of clear synovial fluid. If the aspirate was blood stained, the joint was not used. The radioactive gas xenon (^{133}Xe) (Radiochemical Centre, Amersham) was dissolved in sterile 0·9% sodium chloride and an amount less than 0·5 ml injected into the joint cavity, the needle remaining *in situ* and being closed by a syringe containing 0·9% sodium chloride. Each time an active compound was administered, $< 0{\cdot}25$ ml of ^{133}Xe solution was injected with it. At no time did the total volume injected exceed by more than 50% the amount of synovial fluid aspirated initially.

Counting technique

A lightly collimated detector (Ekco N559 D) incorporating a thallium activated sodium iodide scintillation crystal and photomultiplier was positioned 2 inches from, and directly above the patella. Pulses were fed through a pulse height analyser and ratemeter (Ekco 1750) and recorded on a Rikadenki chart recorder (B24) at a paper speed of 20 mm/min.

The graphs were sampled at 1 min intervals and the absolute count rate was plotted onto semilogarithmic graph paper as a function of time, monitoring being continued throughout each experiment. Baseline values were obtained from the period 1 to 15 min after ^{133}Xe injection, $T\frac{1}{2}$ values (min) being readily obtained from the semilogarithmic plots. As the clearance rate became slower, the semilogarithmic plots approached the horizontal and the errors of calculating the $T\frac{1}{2}$ values were magnified. Accordingly all values in excess of 150 min have been recorded simply as $T\frac{1}{2} = > 150$ min.

The effects of thymoxamine, isoprenaline and noradrenaline alone were studied in groups 1, 2 and 3. Isoprenaline was given after thymoxamine to group 4. Increasing doses of noradrenaline were given after a fixed dose of thymoxamine to group 5, and increasing doses of thymoxamine were given before a fixed dose of noradrenaline to group 6. Increasing doses of thymoxamine were also given after a fixed dose of noradrenaline to Group 7.

Drugs used were: thymoxamine (Warner), (±)-1-noradrenaline acid tartrate (Bayer) and isoprenaline sulphate in normal saline (Boots). These were diluted in sterile 0·9% sodium chloride solution.

RESULTS

The results are shown in Figs 1–3 and Table 1.

In eleven of the twelve studies in Group I (thymoxamine alone, 5, 10, 20 , 30 or 40 μg) the clearance rate after the drug greatly exceeded the baseline value (Table 1).

Table 1. *The effect of thymoxamine, isoprenaline and noradrenaline on the ^{133}Xe clearance rate.*

	Thymoxamine (Group 1)			Isoprenaline 2·5 μg (Group 2)		Noradrenaline 2·5 μg (Group 3)	
	$T\frac{1}{2}$ (min) Before	Dose (μg)	$T\frac{1}{2}$ (min) After	$T\frac{1}{2}$ (min) Before	After	$T\frac{1}{2}$ (min) Before	After
	42	40	26	58	16	66	89
	54	40	28	39	6	54	101
	23	40	17	44	21	38	120
	80	30	38	46	19	47	98
	48	30	38	64	28	42	86
	53	30	31	73	31	49	125
	89	20	42				
	68	20	30				
	44	10	26				
	56	10	38				
	*34	5	30*				
	48	5	16				
Mean	53		30	54	20	49	103
Range	23–89		16–38	39–73	6–31	38–66	86–125
No. showing change		11/ 12 (1 equivocal)		6/6		6/6	

* = equivocal response.

There was no clear relation between effect and the dose used. The remaining result was equivocal. In Groups 2 and 3 the results were consistent: in the six studies with isoprenaline (2·5 μg) the clearance rate after the drug exceeded the baseline values, and in the six studies with noradrenaline (2·5 μg) the clearance rate was reduced after injection (Table 1). Change in clearance rate was abrupt and marked in every instance. When isoprenaline (2·5 μg) was administered after thymoxamine (40 or 200 μg) (Group 4) a marked increase in clearance rate ensued [mean $T\frac{1}{2}$ after thymoxamine (with range) 37 (28–46) at 40 μg; 34 (31–38) at 200 μg, and after isoprenaline 19 (9–26).

The results obtained when increasing doses of noradrenaline (0·5, 1, 2·5, 10 μg) were given after a fixed dose (60 μg) of thymoxamine (Group 5) are in Fig. 1; a dose related response was obtained. When increasing doses of thymoxamine (10, 20, 40, 60, 80, 100 μg) were administered before to a fixed dose (2·5 μg) (Group 6) of noradrenaline, again a dose-related response was obtained (Fig. 2). At a 20 μg dose of thymoxamine, the clearance rate was subsequently abruptly and markedly reduced by noradrenaline. But with thymoxamine 80 or 100 μg no such response to noradrenaline was obtained. Variable responses were noted when the dose of thymoxamine was 40 or 60 μg.

Increasing doses of thymoxamine after noradrenaline (1·0 μg) (Group 7) gave no response until the dose reached 200 μg. Then the clearance rate was abruptly and markedly increased after injection of the thymoxamine (Fig. 3).

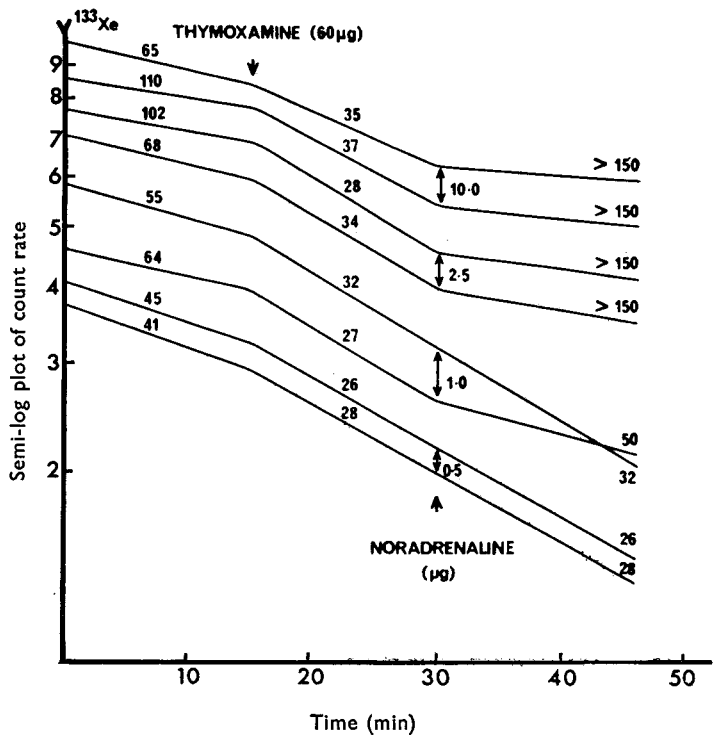

FIG. 1. The effect of increasing doses of noradrenaline after a fixed dose of thymoxamine on the ^{133}Xe clearance rate (Group 5). The $T\frac{1}{2}$ values before and after thymoxamine (60 μg) and after doses of noradrenaline from 0·5–10 μg are shown.

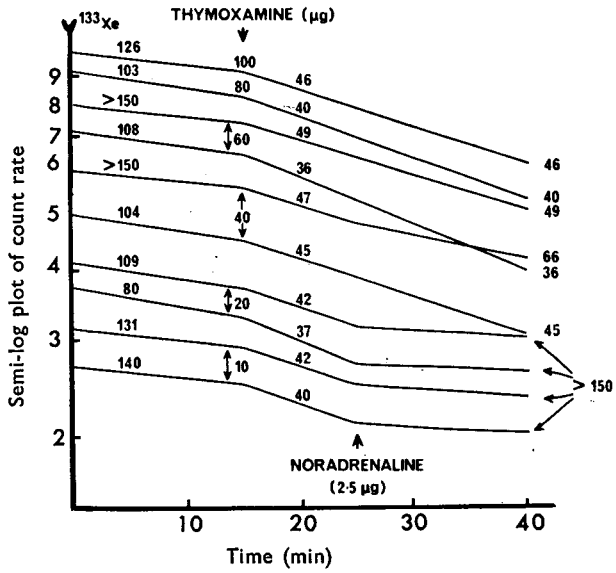

FIG. 2. Effect of increasing doses of thymoxamine before a fixed dose of noradrenaline on the ^{133}Xe clearance rate (Group 6). The $T_{\frac{1}{2}}$ values before and after thymoxamine (10–100 μg) and after noradrenaline (2·5 μg) are shown.

DISCUSSION

The monitoring system used is reproducible (Dick & others, 1970a) and provides an indirect quantitative measure of perfusion (Dick & others 1970b). The term perfusion is appropriate since blood flow through non-nutritive shunts will not be detected (Friedman, 1968). Although the confidence with which the results can be expressed in absolute units of perfusion cannot be complete because the method is

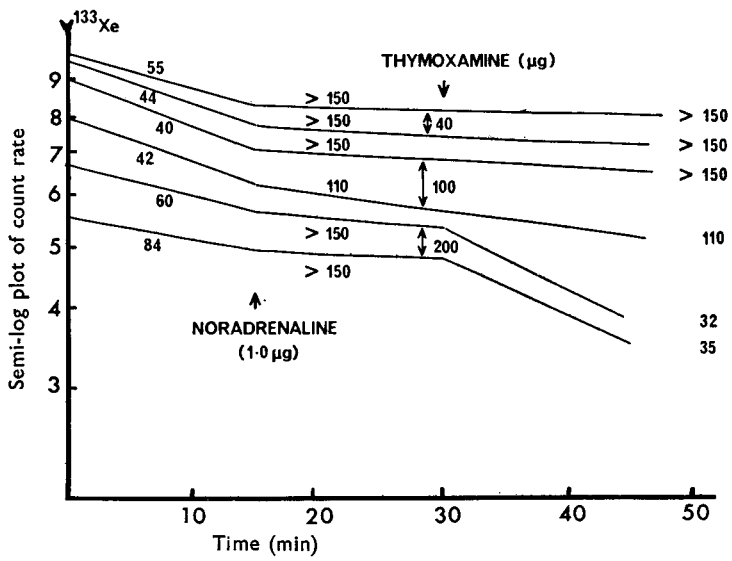

FIG. 3. Effect of increasing doses of thymoxamine after a fixed dose of noradrenaline on the ^{133}Xe clearance rate (Group 7). The $T_{\frac{1}{2}}$ values before and after noradrenaline (1 μg) and after thymoxamine (40–200 μg) are shown.

indirect and no other method is available for confirmation, the large changes in clearance rate associated with drug administration may be attributed to pharmacologically induced changes in perfusion. The results may be interpreted to indicate that whereas noradrenaline reduces synovial perfusion, intra-articular isoprenaline and thymoxamine increase clearance rate and therefore synovial perfusion rate. The results with noradrenaline, and with isoprenaline, are explicable in terms of their known effects on other vascular beds (Goodman & Gilman, 1965), but interpretation of the effect of thymoxamine is less obvious. Increase in clearance rate, and in perfusion rate may be the result of a direct effect of the drug on small blood vessels. But the evidence for this is inconclusive. A further possibility supported by the conclusions of Birmingham, Akubue & Szolcsányi (1967) and Turner, Harrison & Schoenfeldt (1969) is that the compound releases these peripheral vessels from a basal α-adrenergically mediated vasoconstrictor tone, which has been demonstrated previously in canine joints (Cobbold & Lewis, 1956).

The results also demonstrate that whereas thymoxamine has no influence on β-adrenergically mediated isoprenaline response, the drug will abolish the α-mediated effect of noradrenaline. The effect is dose related and can be modified by either increasing the dose of the agonist or reducing the dose of the blocking agent. Furthermore, the noradrenaline effect can be reversed by a large dose of thymoxamine. These results support the views of Birmingham & Szolcsányi (1965) that the mode of action of thymoxamine is by competitive antagonism. The dose ratio at which the modifying effect of thymoxamine was seen varied. When thymoxamine was given first (Groups 5 and 6) the dose ratio was about 60 (thymoxamine) to 1 (noradrenaline). However, when noradrenaline was given first the corresponding ratio was 200:1. Variation in affinity of the compounds for the receptor binding sites may explain this discrepancy.

It would seem from the results that the ^{133}Xe clearance technique provides a suitable model for the *in vivo* study of pharmacologically induced changes in perfusion. The method is particularly attractive since it involves only minimal interference with the physiological state of the animal.

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