Subjects again rested supine, and were given 5 mg practolol intravenously. The sequence of observations was repeated, and again following a further 15 mg practolol (incremental total 20 mg), again after another 60 mg (80 mg total), and again after 80 mg (160 mg total). Blood pressure was taken by the London School of Hygiene and Tropical Medicine sphygmomanometer (Rose, Holland & Crawley, 1964) and heart rate was recorded by an electrocardiogram.

Resting pulse was unchanged; there was progressive reduction in the tachycardia induced by isoprenaline and by endogenously induced sympathetic activity (see Table 1). Results have been expressed in terms of the final pulse rate reached from

TABLE 1

| | Resting pulse | Tachycardia induced by isoprenaline 4 μg/min | Tachycardia end effort Valsalva (40 mm Hg for 20 s) | Tachycardia exercise 100 watts for 2 min |
|---|---|---|---|---|
| Control | 73 | 104 | 105 | 120 |
| $n=6$ | | N.S. | $P<0{\cdot}01$ | N.S. |
| After practolol | | | | |
| 5 mg | 72 | 103 | 99 | 116 |
| $n=5$ | | $P<0{\cdot}05$ | $P<0{\cdot}005$ | $P<0{\cdot}05$ |
| 20 mg | 72 | 97 | 89 | 111 |
| $n=6$ | | $P<0{\cdot}005$ | $P<0{\cdot}05$ | $P<0{\cdot}01$ |
| 80 mg | 72 | 88 | 84 | 105 |
| $n=6$ | | N.S. | $P<0{\cdot}05$ | N.S. |
| 160 mg | 75 | 87* | 81 | **105 |
| $n=5$ | | | | |

* Average pulse rate reduction between 80 mg and 160 mg=4·2 in five patients receiving both dose levels of practolol.

** Average pulse rate *reduction* between 80 mg and 160 mg=1·8 in five patients receiving both dose levels of practolol.

*P* values indicate the probability of a difference between the figures immediately above and below.

the stimulus concerned. Calculations based on the increment in pulse rate to each stimulus show a similar pattern. By extrapolation, the isoprenaline dose required to increase the pulse rate by 20 beats/min shows no change after 5 mg practolol but a dose dependent relationship is apparent at increasing doses of practolol. Log/dose response curves suggest competitive inhibition by practolol both in response to challenge by isoprenaline and endogenously liberated catecholamine. Assessment of the changes in blood pressure makes it appear unlikely that reflex vagal changes are responsible for the results.

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## The fate of isoprenaline administered by pressurized aerosols

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The cardiac response to an inhaled dose of isoprenaline can be reproduced by administering approximately 2% of the same dose intravenously. It has not previously been determined whether this is because the major part of the isoprenaline inhalation is swallowed and inactivated or because it is inactivated in the bronchi.

Studies have been undertaken in two patients and three volunteers using specially prepared " medihalers " loaded with $^{3}$H-isoprenaline, designed to deliver 500 $\mu$g per dose. Arterial blood samples were taken in four of the studies, at timed intervals immediately after the inhalation. Urine was collected for 48 h after administration of the $^{3}$H-isoprenaline.

In no subject was a pharmacological response detected. In three subjects no radioactivity was found in the arterial blood. In the other, radioactivity equivalent to isoprenaline 0·3 ng/ml was detected 5 min after inhalation.

Two of the normal subjects excreted 96 and 97·25% of the total dose in the urine over 48 h. In a third subject, in whom collections were incomplete, only 48% of the dose was recovered, but the pattern of metabolite excretion was the same.

The urinary radioactivity comprised conjugated isoprenaline (81–95%) conjugated 3-O-methyl isoprenaline (4–6%), free isoprenaline (1–2%) and free 3-O-methyl isoprenaline (1–2%).

The pattern of metabolism following administration of isoprenaline from the " medihaler " is similar to that seen after small oral doses (0·5 mg isoprenaline) administered to three other subjects in which the urinary radioactivity was mainly conjugated isoprenaline (68–94%). The remainder of the radioactivity was conjugated 3-O-methyl isoprenaline (2–8%), free isoprenaline (4%) and free 3-O-methyl isoprenaline (0–1%). The pattern of metabolism in both studies differs from that seen after intravenous administration, in which up to 30% of the isoprenaline is excreted as 3-O-methyl isoprenaline, and none as the conjugate of isoprenaline.

The conclusion from this study is that most of the isoprenaline taken from a pressurized aerosol is swallowed.

**The effects of dopamine, L-dopa, L-tyrosine, and pyridoxine on sympathetic nerve endings in man**

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The normal human eye has been used as a model for investigating the mechanism of action of L-dopa and related substances in volunteer subjects. Eye drops of L-dopa (1·0% w/v in borate buffer) and dopamine (10% w/v in bicarbonate:sulphite buffer) produce marked mydriasis. Solutions of L-tyrosine (0·06% w/v in borate buffer) have no detectable effects. Prior treatment with 5% guanethidine eye drops (Ismelin eye drops; Ciba) reduced or abolished the mydriatic response to L-dopa or dopamine in five out of twelve subjects. Persisting response to dopamine or L-dopa after guanethidine pre-treatment in the remaining seven subjects was associated with preservation of the mydriatic response to tyramine (2% w/v in borate buffer). These results suggest that the mydriatic action of dopamine and L-dopa, like that of tyramine, is indirect, depending on release of noradrenaline from sympathetic nerve endings. Probable depletion of noradrenaline in the sympathetic nerve endings of the iris by guanethidine eye drops inhibits the action of all these drugs. In six out of forty subjects, mydriasis produced by dopamine or L-dopa waned gradually despite continued instillation of the drug into the conjunctival sac. This decreasing mydriasis may reflect depletion of available noradrenaline stores.