Pholedrine: a substitute for hydroxyamphetamine as a diagnostic eyedrop test in Horner’s syndrome

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Abstract
Mydriatic responses to eyedrops containing the indirect acting sympathomimetic amines tyramine, hydroxyamphetamine, and pholedrine have been compared in 10 healthy subjects. Pholedrine, the n-methyl derivative of hydroxyamphetamine, at a concentration of 1% had effects similar to those produced by 0.5% hydroxyamphetamine itself. Pretreatment with topical guanethidine attenuated its responses and in 13 patients with unilateral Horner’s syndrome it distinguished clearly those five patients who had preganglionic from the eight with postganglionic lesions. It is concluded that 1% pholedrine may be substituted for 0.5% hydroxyamphetamine, which is no longer available, as a diagnostic agent for use in Horner’s syndrome.

(J Neurol Neurosurg Psychiatry 1995;58:215–217)

Keywords: Horner’s syndrome; hydroxyamphetamine; pholedrine

In most instances of unilateral Horner’s syndrome the site of the sympathetic lesion, whether preganglionic or postganglionic, can be gauged from the diagnosis of the prevailing clinical condition. Nevertheless, it is sometimes helpful to have a confirmatory indication of the site from a pharmacological eyedrop test. Thus the sympathomimetic agent hydroxyamphetamine has for some years been used for this purpose.1 2 It acts indirectly by releasing stored noradrenaline from terminals of the postganglionic nerve,3 and its effect depends, therefore, on the functional integrity of the third neuron. When the drops are placed in both eyes of a patient with unilateral Horner’s syndrome, failure of the affected pupil to respond and a consequent increase in the existing anisocoria indicate that the lesion is postganglionic. By contrast, a positive response of the affected pupil, without change in or even reversal of the anisocoria, show that it is preganglionic. The results of the test are usually clearcut, although in a small proportion of patients, including presumably ones in whom the neurological lesion is mixed or incomplete, the result is inconclusive.4 5 The precision of the test depends at least in part on the cut off point used to determine what constitutes a positive mydriatic response.

Hydroxyamphetamine is no longer obtain-
Kline and French), tyramine hydrochloride (Sigma), pholedrine sulphate (Knoll). Concentrations used refer to weights of the salts.

**PUPIL MEASUREMENTS**

Vertical pupil diameters of both eyes were recorded in the light with a Whittaker Series 800 binocular infrared television pupillometer as previously described. Measurements were taken before and at 10 or 15 minutes intervals after eyedrop instillation until maximum drug effects had been reached (usually at 45–60 minutes).

**Results**

Hydroxyamphetamine, pholedrine, and tyramine produced dose dependent mydriasis (fig 1), although in each case the highest concentrations tested produced submaximal responses. From the linear portion of the log concentration relation the mean potencies relative to hydroxyamphetamine were pholedrine 0.62 and tyramine 0.047. Subjects with darkly pigmented irides showed significantly less mydriasis to all three agents than did those with blue or hazel coloured irides ($F = 41.676$, $p < 0.001$), responses to the optimal dose of pholedrine being reduced to about that of half the dose. On the basis of these results and the previous use of 0.5% hydroxyamphetamine as a diagnostic test, it was decided to employ pholedrine at a concentration of 1% and to apply single eyedrops to subjects with light coloured irides, two drops to those with darkly pigmented irides.

In healthy subjects given guanethidine eyedrops the treated pupil was smaller than the untreated one, the anisocoria ranging from 0.5 to 2.3 mm. Pholedrine produced a greater mydriatic response in the untreated than in the guanethidine treated eye. As a result, in every case the anisocoria increased (fig 2); the mean increase was 1.3 (SEM 0.3) mm.

In patients with Horner's syndrome due to postganglionic lesions, pholedrine produced a greater mydriatic response in the normal than in the affected eye. As a result, in every case the magnitude of the anisocoria increased (fig 3, left); the mean increase was 1.7 (SEM 0.3 mm). In four of the patients with postganglionic lesions, pholedrine produced similar responses in the two eyes; in the fifth, the anisocoria disappeared. Overall, no increase in the anisocoria occurred (fig 3, right), the mean change being −0.24 (SEM 0.27 mm). There was no overlap in response between patients with lesions in the two locations. The greatest increase in postganglionic cases was 0.2 mm and the least in postganglionic cases was 0.8 mm. The difference between the responses was statistically significant ($t = 5.050$, $p = 0.001$).

**Discussion**

These findings indicate that, like hydroxymphetamine, pholedrine applied as 1% eyedrops produces mydriasis that is greatly attenuated by guanethidine pretreatment and diminished in patients with postganglionic sympathetic nerve lesions. This finding was anticipated because of the close structural similarity of the two drugs (pholedrine is the N-methyl derivative of hydroxymphetamine) and the indirect nature of their sympathomimetic action. It can therefore be regarded as a satisfactory substitute for hydroxymphetamine as an eyedrop test for localisation of the lesion in cases of unilateral Horner's syndrome. Similar findings, using pholedrine at the much higher concentration of 5%, have been reported recently.

In clinical practice some hydroxymphetamine tests on patients with unilateral Horner's syndrome yield inconclusive results, even when the site of the lesion is clearly defined. If pholedrine is used as a substitute, it is unlikely to prove more selective. Consequently, it is recommended that the test should continue to be used as no more than a diagnostic aid.
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We are grateful to the Iris Fund for the Prevention of Blindness for financial support and Knoll Ltd, Maidenhead for supplying pholedrine sulphate.