EPHEDRINE AND PSEUDO-EPHEDRINE IN ASTHMA, BRONCHIAL ASTHMA, AND ENURESIS*

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The work here described was part of an inquiry arranged by the Therapeutic Trials Committee into the relative values of ephedrine and pseudo-ephedrine. The ephedrine and pseudo-ephedrine hydrochloride used in the tests were supplied to the committee by Messrs. Burroughs Wellcome and Co., who also provided a quantity of inert tablets for use as controls.

The comparative pharmacology of ephedrine and pseudo-ephedrine is discussed in detail elsewhere in a paper by Dimson.¹ The two alkaloids occur together in varying proportions in the several species of *Ephedra* used commercially for the manufacture of ephedrine. They have the same chemical structure—namely, $C_6H_5 \cdot CHOH \cdot CH(NH \cdot CH_3) \cdot CH_3$. There is, however, a physical distinction between the two, ephedrine being laevorotatory and pseudo-ephedrine dextrorotatory. On the basis of the findings with regard to other optical isomers, such as *l*- and *dl*-hyoscyamine, it might be expected that ephedrine and pseudo-ephedrine would have similar qualitative actions but would differ quantitatively. Clinical evidence may be said generally to support this view.

Before the trials were begun the actions of ephedrine and pseudo-ephedrine had been compared in India by Chopra, Krishna, and Ghose,² who reached the following main conclusions:

1. Both ephedrine and pseudo-ephedrine have a pressor action, the former being more powerful than the latter.
2. Pseudo-ephedrine is less toxic than ephedrine.
3. The dilator action of pseudo-ephedrine on the bronchioles is nearly as marked as that of ephedrine; and so is its constricting action on the mucous membrane of the nose. Both ephedrine and pseudo-ephedrine are useful in asthma, the latter having the advantage of producing fewer "side-effects."
4. Pseudo-ephedrine is more powerfully diuretic than ephedrine.

Apart from observations on a few ambulant cases of asthma, the blood pressures in which were subnormal, we have not explored the pressor action of these drugs. They have recently been carefully compared in patients by Dimson¹ and by Monro.³ The findings of these workers, and our own so far as they go, support the conclusions of other investigators that the pressor action of pseudo-ephedrine is much less than that of ephedrine.

Our inquiry has been directed mainly to the action of ephedrine and pseudo-ephedrine in asthma, in "chronic bronchitis," and in enuresis. In the course of this work we have naturally had an opportunity of comparing the toxicity of the two isomers, and of observing incidentally their supposed diuretic actions. It may be said at once, however, that, although we have not used pseudo-ephedrine intentionally as a diuretic where such was indicated, we have obtained no evidence in our inquiry

that it acts in this way in patients with normal cardiovascular systems. None of our patients has complained of increased frequency of micturition when taking it; in fact, the converse has, in a sense, been true, for pseudo-ephedrine has been used with success in the treatment of enuresis in children.

Comparative Tests in Spasmodic and in Bronchial Asthma

For the purposes of this study we have classified our asthmatic patients on the basis of symptoms and routine clinical examination into: (a) "spasmodic" cases—that is, cases without gross evidence of bronchitis, etc.; and (b) "bronchial" cases—that is, cases with gross evidence of bronchitis, etc.

SPASMODIC ASTHMA

Twenty-four cases of this type were treated successively with ephedrine and pseudo-ephedrine, with an interval between the two drugs, during which the patients were treated with inert tablets made to resemble those previously given. Ten of the patients were under the age of 10. Both ephedrine and pseudo-ephedrine were ordinarily given at bedtime in doses of 1/4 to 2 grains, according to the age of the patient and the reactions obtained: when necessary, however, the same dose was repeated in the morning on waking, or later in the day. The results may be summarized as follows: Five had no bad attacks during the whole period of observation. Fifteen were relieved of wheezing and dyspnoea both by ephedrine and by pseudo-ephedrine, but pseudo-ephedrine was less effective than ephedrine in relieving definite attacks. Four were relieved of wheezing and dyspnoea by taking pseudo-ephedrine every night. In these, pseudo-ephedrine was also effective in the attacks when they appeared, but less promptly than ephedrine in the same dosage.

BRONCHIAL ASTHMA*

The results in thirty-seven cases of this type were as follows. In eight, pseudo-ephedrine was not effective for acute attacks, though useful for chronic dyspnoea and wheezing. In nine, pseudo-ephedrine, in addition to its use in preventing attacks, was also effective in relieving slight attacks. Twenty patients had no severe attacks, and in fifteen of these pseudo-ephedrine, taken regularly, relieved nocturnal dyspnoea and wheezing.

It should be mentioned, incidentally, that thirty-two of our cases of spasmodic and bronchial asthma were also under treatment with sodium iodide throughout the inquiry. We have found this drug of definite value in the prophylaxis of asthmatic attacks. Our usual procedure is to give 30 grains at 6 p.m. and at bedtime. To more obstinate cases we also give 30 grains sodium iodide intravenously once a week. Complete immunity from severe attacks may be obtained for many months with this medication, but, in our experience, most patients need an additional safeguard in order to obtain freedom from nocturnal wheezing and dyspnoea. We have found both ephedrine and pseudo-ephedrine useful for this purpose, pseudo-ephedrine being frequently the more satisfactory on account of its lower toxicity. Of nineteen cases which gave a definite response to pseudo-ephedrine and were not under the influence of sodium iodide, twelve had relief from nocturnal dyspnoea when taking pseudo-ephedrine 1/2 grain regularly at bedtime; the remainder required 1 to 2 grains, according to the severity of their symptoms.

* In this group we have included, as stated, all the cases under observation in which asthmatic attacks were associated with gross evidence of chronic bronchitis. But, in the view of one of us (J. B. C., *Amer. Journ. Med. Sci.*, 1933, clxxxvi, 504), the disorder known as "chronic bronchitis" itself needs reviewing and reclassifying in relation to modern knowledge. For the accurate sorting out of the different conditions at present labelled "chronic bronchitis" on clinical grounds, a lipidol examination of the lungs is necessary.

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It may be said generally that pseudo-ephedrine is useful in any case of wheezing and dyspnoea due to spasmodic constriction in the bronchial tree. We have also found it of value in the chronic "exertion" dyspnoea associated with severe fibrosis of the lung, as in tubercle or bronchiectasis.

Toxic Effects of Ephedrine and Pseudo-Ephedrine Compared

Toxic reaction to ephedrine in small doses is more frequent than is perhaps generally realized. It leads many patients to delay taking the drug until the asthmatic attack actually appears—when ephedrine, compared with asthma, is regarded as the lesser of two evils. This reluctance to take ephedrine as a prophylactic is unfortunate, since experience shows that the greatest value of this drug is as a preventive. If, therefore, pseudo-ephedrine could be shown to be nearly as good as ephedrine in this respect, while being less toxic, it would have obvious clinical value in the routine treatment of asthma.

We found that the toxic symptoms produced by ephedrine and by pseudo-ephedrine were similar in nature, but differed in frequency of occurrence and in the dosage necessary to induce them. Thus in sixty-one asthmatic or bronchitic patients treated with both drugs thirty-two showed hypersensitivity to ephedrine, sixteen to pseudo-ephedrine, and thirteen to both. Of the thirty-two cases which showed hypersensitivity to ephedrine three had toxic symptoms with doses of $1/4$ grain, twenty-three with $1/2$ grain, and six with 1 grain. Of the sixteen cases which were hypersensitive to pseudo-ephedrine one had toxic symptoms with doses of $1/4$ grain, eleven with $1/2$ grain, and four with 1 grain.

Palpitation of the heart was the most frequent unpleasant reaction both with ephedrine and with pseudo-ephedrine. After that came insomnia or restlessness during sleep. Nausea or gastric pain was the most frequent unpleasant reaction in children under 14. Then came certain nervous symptoms: "queer head," giddiness, trembling, sweating, "cold and sleepy feeling," "cramp" in fingers, tingling feeling in skin.

In fifteen cases pseudo-ephedrine seemed to have had an equal physiological effect with ephedrine in the same dosage. Of these, seven showed slight toxic or unpleasant reactions, distributed as follows: four with ephedrine, three with both ephedrine and pseudo-ephedrine, none with pseudo-ephedrine only. The common dosage in these cases was: in ten cases, $1/2$ grain, in five cases 1 grain. One of the fifteen had toxic symptoms at first after ephedrine, but after a course of pseudo-ephedrine toxic symptoms seemed to be less marked with ephedrine. In fourteen cases ephedrine was more effective than pseudo-ephedrine, but produced more unpleasant reactions. In these the doses of pseudo-ephedrine were double those of ephedrine, and one patient, a boy of 6, had slight toxic reaction (restless night) after pseudo-ephedrine $1/2$ grain. There is no doubt that in order to get the same physiological effect pseudo-ephedrine must ordinarily be used in larger doses than ephedrine. As a general rule $1/2$ grain is a usual dose of ephedrine for an adult, whereas 1 or 2 grains of pseudo-ephedrine has to be given to produce a corresponding physiological effect.

Four cases appeared to be resistant to pseudo-ephedrine though they responded well enough to ephedrine. In one of these pseudo-ephedrine produced unpleasant reactions. Forty-four cases of the total were definitely responsive to pseudo-ephedrine in doses of $1/2$ to 2 grains, but only in fifteen could it be maintained that pseudo-ephedrine had an equal physiological effect to ephedrine, and seven of these had slight toxic symptoms with one or both drugs. In nine cases where pseudo-ephedrine was effective but less so than ephedrine no toxic or unpleasant reactions occurred with either drug.

Ephedrine and Pseudo-Ephedrine in Enuresis

We have recently treated cases of enuresis with ephedrine, either alone or in conjunction with an alkaline belladonna mixture, and have obtained very satisfactory results. Our attention was first called to this treatment by a letter in the *British Medical Journal* by L. E. Parkhurst.⁴ He gave ephedrine $1/2$ grain at bedtime to children aged 10 to 12, and claimed that the treatment was "almost specific." In view of the response to pseudo-ephedrine in the majority of our cases of asthma it seemed of interest to determine whether this isomer was also effective in enuresis.

Our experiments with pseudo-ephedrine were carried out on children varying in age from 3 to 13, all of whom were attending a hospital out-patient department. Altogether twelve patients were treated during periods varying from one to four months. Of these cases eight were controlled by ephedrine $1/4$ grain given at bedtime without other treatment, and four were more severe and needed ephedrine $1/2$ grain at bedtime with an alkaline belladonna mixture by day. One of these four appeared to depend more upon the belladonna mixture than upon the ephedrine, though the giving of ephedrine $1/2$ grain at bedtime seemed definitely to increase the power of control; the same applied when pseudo-ephedrine 1 grain was given at night.

Speaking generally, the substitution of pseudo-ephedrine for ephedrine in the same dosage slightly decreased the extent of control, maintaining it at a somewhat lower level. Thus in seven of the eight cases controlled by ephedrine $1/4$ grain pseudo-ephedrine had to be given in doses of $1/2$ grain to produce a satisfactory result. Only one of these responded to $1/4$ grain of pseudo-ephedrine. Similarly, of the four cases on ephedrine $1/2$ grain plus the alkaline belladonna mixture, two required 1 grain of pseudo-ephedrine plus the mixture; the other two kept well on $1/2$ grain. One patient to whom no ephedrine had previously been given improved at once with pseudo-ephedrine $1/4$ grain at night and responded completely to $1/2$ grain. In three patients, who had incontinence by day as well as by night, an additional dose of ephedrine or pseudo-ephedrine was given in the morning with benefit. No symptoms suggesting intolerance were complained of by these patients or noticed by their parents after either drug. It appears, therefore, that effective doses may be given to children quite confidently, and pseudo-ephedrine may be considered a useful addition to the somewhat limited therapeutics of enuresis.

Conclusions

1. Pseudo-ephedrine is valuable as a gentle bronchial sympathetic stimulant sufficiently active to give relief in chronic cases of wheezing and dyspnoea.
2. It is a useful prophylactic against the nocturnal dyspnoea of asthma and against the dyspnoea of exertion in chronic bronchitis.
3. It does not effectively take the place of ephedrine, still less of adrenaline in acute attacks of asthma.
4. It is non-cumulative in its action, and produces fewer "side-effects" than ephedrine in the same or rather larger dosage.
5. Generally speaking, though not always, about double the dosage of pseudo-ephedrine is required to produce the equivalent physiological effect of a given dose of ephedrine.
6. In cases of enuresis in children pseudo-ephedrine is also useful, though perhaps not quite equal to ephedrine, which we consider to have high value in this condition.

REFERENCES

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