EFFECTS ON THE HUMAN CENTRAL NERVOUS SYSTEM OF TWO ISOMERS OF EPHEDRINE AND TRIPROLIDINE, AND THEIR INTERACTION

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1 D(-)ephedrine is four times as potent as L(+)-pseudoephedrine in producing both tachycardia and a rise in systolic blood pressure. No changes in diastolic blood pressure occurred in 12 subjects with doses of up to D(-)ephedrine (50 mg) and L(+)-pseudoephedrine (180 mg).

2 Significant evidence of stimulation of the central nervous system occurred only after D(-)ephedrine in that tapping rates were increased and subjects could reliably detect that they had received an active drug. While mean performance rates in an auditory vigilance test were higher following both ephedrine isomers these changes were not significant.

3 Impairment of both tapping rates and auditory vigilance occurred following triprolidine in another group of 12 subjects. The effect was generally related to dose of antihistamine given and lasted up to 7.25 hours. Subjective effects were reliably recognized by subjects following all treatments containing triprolidine (2.5 mg or more) for up to 4.75 hours. Using analogue lines for self rating the subjective effects following triprolidine indicated both mental and physical impairment differing significantly from scores after lactose and L(+)-pseudoephedrine (60 mg).

4 Combination of triprolidine (2.5 mg) and L(+)-pseudoephedrine (60 mg) produced effects similar to triprolidine alone on both subjective measures and the auditory vigilance test. It is suggested that these objective tests and subjective scales could be used to measure effects on the central nervous system produced by antihistamines together with similar drugs, and their interaction with other compounds administered concurrently.

Introduction

Of the four possible stereoisomers of ephedrine shown in Fig. 1 only D(-)ephedrine and L(+)-pseudoephedrine are in current therapeutic use. D(-)ephedrine is used chiefly for its bronchodilator effects while L(+)-pseudoephedrine is used chiefly as a nasal decongestant either alone (Sudafed & Sanco Co.), or in combination with antihistamines such as triprolidine (Actifed). Insomnia due to mild stimulation of the central nervous system during treatment with D(-)ephedrine is a well recognized side effect in asthmatic patients. Much rarer are cases of psychosis induced by excessive use of D(-)ephedrine which closely resemble the more common amphetamine psychosis (Herridge & a'Brook, 1968; Prokop, 1968; Bartoszewski & Majewska, 1972). By contrast, drowsiness is a well recognized side effect of effective antihistamines, but attempts to measure this phenomenon and compare the relative effects of different drugs have not been made. In view of this it was decided to investigate the central effects of the two ephedrine isomers, triprolidine, and a

combination of L(+)-pseudoephedrine and triprolidine using an experimental design and test procedures which had previously proved extremely sensitive to dexamphetamine in our hands (Bye, Munro-Faure, Peck & Young, 1973).

Methods

Subjects

Twelve healthy paid volunteers were used in each of two separate trials. In Trial 1, two ephedrine isomers were administered to 11 men and one woman aged from 22-37 years, and in Trial 2, L(+)-pseudoephedrine and triprolidine were administered to seven men and five women aged from 24-43 years. They were transported to and from the laboratory by car, and were not allowed tea, coffee, cigarettes or alcohol on the experimental days until completion of the tests. No breakfast other than fruit juice was allowed, and

Fig. 1 Structures of the 4 isomers of ephedrine (after Patil, Tye & LaPidus, 1965).

food intake through the day, while not identical, was similar on different occasions.

Tests

A test schedule lasting 2.5 h, beginning 30 min after each treatment and repeated three times, was used in both trials. The schedule in Trial 1 consisted of the following tests in order:

(a) A visual search test lasting 30 min in which subjects systematically searched pages of random letters for the five specified letters on each page, and on completion moved to the next page. The number of pages completed were counted.

(b) A digit symbol substitution test derived from Wechsler (1955) lasting 90 seconds. The number of items correctly completed and number of errors were counted.

(c) The tapping test counted for 1 minute.

(d) An auditory vigilance test devised by Wilkinson (1968) and described in detail by Bye *et al.* (1973) in which the subject listens for 1 h to short tones 0.5 s in duration occurring every 2 seconds. The signals to be detected are tones of 0.4 s, 10 of which occur randomly in each quarter hour. Subjects also rate their confidence in any particular signal into high, medium or low.

(e) Heart rate (radial pulse) and blood pressure (using sphygmomanometer) both taken while supine after 10 min rest.

(f) Subjective effects were measured using the analogue line technique described by Norris (1971), in which the subject records his mental state by marking a series of 100 mm lines indicating the dimensions of mental state shown in Table 4. In addition subjects were asked whether they thought that they had received an active drug.

(g) A rest period of 30 min before repeating the schedule.

In Trial 2 the test schedule differed only in that heart rate and blood pressure were not measured. Instead, unstimulated salivary secretion over a 5 min period was measured by weighing, pupil size was measured photographically using constant illumination, and visual near point was measured. All tests and measurements except heart rate and blood pressure were made in a soundproof room maintained at 70°F. No information on performance of test was given to the subjects until after completion of the investigation.

Drugs

In both trials all subjects received six treatments administered orally in identical soft gelatin capsules, at weekly intervals under double blind conditions according to a balanced design based on two six sided Latin squares. In Trial 1 the treatments were: D(-)ephedrine hydrochloride, 25 and 50 mg; L(+)pseudoephedrine hydrochloride 60, 120 and 180 mg; and a lactose dummy. In Trial 2 the treatments were: triprolidine 1.25, 2.5 and 5.0 mg; L(+)pseudoephedrine 60 mg; a combination of triprolidine 2.5 mg and L(+)pseudoephedrine 60 mg; and a lactose dummy. All treatments were given at 09.00 hours.

Analysis of results

All autonomic and behavioural measurements were subjected to analysis of variance. Subjective effects obtained from the position of the mark on the 100 mm line were converted by arc-sine transformation of the score to provide a theoretically more normal distribution. Transformed scores were then submitted to analysis of variance for each dimension. For each of the three post drug sessions factors for drugs, occasions, and subjects were considered and drug means compared by Duncan's test where significant differences were indicated. Changes in the proportions of subjects responding 'yes' or 'no' and 'doubtful' when asked if they received an active drug following different

treatments, were compared with the proportion following the lactose dummy using Fisher's exact probability test for the double dichotomy situation. Throughout, values achieving $P < 0.05$ were taken as significant.

Results

Autonomic variables

The cardiovascular measures made in Trial 1 and the basal salivary secretion measured in Trial 2 are illustrated in Table 1. Significant rises occurred in heart rate ($P < 0.01$) 2.5, 5.0 and 7.5 h after both doses of D(-)ephedrine and L(+)-pseudoephedrine (120 and 180 mg). Systolic blood pressure also rose significantly after these doses, the D(-)ephedrine being four times as potent as L(+)-pseudoephedrine, and the duration of effect less than on heart rate. There were no effects on diastolic blood pressure. Basal salivary secretion was lower following all treatments at 2.5, 5.0 and 7.5 h but the individual values were not significantly reduced. Mean values for all three post-drug sessions, however, for triprolidine (2.5 and 1.25 mg) and the combination of L(+)-pseudo-

ephedrine and triprolidine were significantly lower than following lactose.

There were no significant changes in visual near point or pupil size ascribable to differences in treatment.

Performance tests

Significant changes occurred in tapping rates and auditory vigilance and these are illustrated in Table 2 and Figure 2.

Tapping rate. This was significantly ($P < 0.01$) raised following both doses of D(-)ephedrine 1 h post-treatment but not after any doses of L(+)-pseudoephedrine in either trial. Rates following triprolidine (2.5 and 5.0 mg) were significantly lower than after lactose and L(+)-pseudoephedrine (60 mg), at 1 h, and on combination of all three post-treatment tests. The performance following combined L(+)-pseudoephedrine (60 mg) and triprolidine (2.5 mg), occupied an intermediate position, not differing significantly from either drug administered alone.

Auditory vigilance. During the period 1.25-2.25 h post-treatment the percentage correct

Table 1 Mean values of heart rate, blood pressure and salivary secretion are shown for 12 subjects.

Trial 1	Lactose	D(-)ephedrine			L(+)-pseudoephedrine		
		50 mg	25 mg	180 mg	120 mg	60 mg	
Heart rate (beats/min)							
Time after drug 2.5 h	61	68**	68**	66**	66**	64	
5.0 h	67	77**	72**	73**	71*	70	
7.5 h	66	72**	74**	73**	72**	68	
Systolic B.P. (mmHg)							
2.5 h	113	130**	120*	128**	121*	120*	
5.0 h	114	121*	122*	122*	115	117	
7.5 h	116	122*	120	121	117	119	
Diastolic B.P. (mmHg)							
2.5 h	70	70	67	76	71	74	
5.0 h	66	62	62	65	66	64	
7.5 h	67	64	65	66	65	67	
Trial 2	Lactose	5 mg	Triprolidine		Pseudoeph. (60 mg) and triprol. (2.5 mg)	Pseudoeph. (60 mg)	
			2.5 mg	1.25 mg			
Salivary secretion (g/5 min)							
Time after drug 2.5 h	3.5	2.8	2.6	2.8	2.4	3.1	
5.0 h	2.9	2.4	2.0	2.4	2.2	2.7	
7.5 h	3.1	2.7	2.6	2.6	2.4	2.8	
Mean of three sessions	3.2	2.7	2.4*	2.6*	2.3*	2.8	

The statistical significance of differences following different treatments, from those following lactose are indicated by ** or *

Table 2 Mean values in the tapping test and auditory vigilance test for 12 subjects for each of the six treatments are shown, and are ranked in ascending order.

	Trial 1						Trial 2					
	L	P60	P180	P120	E25	E50	T2.5	T5	C	T1.25	L	P60
Tapping test (1 min)												
1 h post drug	374	375	378	382	391	395	347	349	359	359	363	365
Mean of three post drug tests	P60	L	P120	P180	E25	E50	T5	T2.5	T1.25	C	L	P60
	370	373	375	376	386	386	349	351	353	354	360	361
Auditory vigilance (% correct detections over 1 h test)												
1.25-2.25 h post drug	L	P60	P180	E25	P120	E50	T5	T2.5	T1.25	C	L	P60
	49.8	53.5	54.0	55.0	56.5	58.5	36.5	48.3	48.8	49.4	55.8	60.6
3.75-4.75 h post drug	E50	E25	L	P60	P180	P120	T5	T1.25	C	T2.5	L	P60
	48.8	49.0	49.6	50.2	50.8	52.3	33.3	41.3	42.5	43.8	49.8	53.8
6.25-7.25 h post drug	L	P60	E25	E50	P180	P120	T5	C	T2.5	T1.25	P60	L
	51.7	53.8	54.0	55.6	56.0	56.3	41.7	41.7	47.9	49.0	54.4	55.4

Abbreviations used are: D(-)ephedrine (25 and 50 mg), E25 and E50; L(+)pseudoephedrine (60, 120 and 180 mg), P60, P120 and P180; triprolidine (1.25, 2.5 and 5.0 mg), T1.25, T2.5 and T5; combined L(+)pseudoephedrine (60 mg) and triprolidine (2.5 mg), C; lactose dummy, L. Mean values which do not differ significantly are underlined by a common line. Where no common line exists between two or more treatment means, then they differ at $P < 0.05$.

Fig. 2 Mean values for % signals detected by 12 subjects in the auditory vigilance test are shown on the ordinate. Values for each 15 min of the first 1 h test after treatment are shown. The different treatments are: (○) lactose; (●) L(+)-pseudoephedrine 60 mg; (■) triprolidine 5 mg; (□) triprolidine 2.5 mg; (▲) L(+)-pseudoephedrine 60 mg and triprolidine 2.5 mg combined. Performance following triprolidine 1.25 mg has been omitted for clarity.

detections following both ephedrine isomers were higher than following lactose. Any differences, however, were small and failed to reach the $P < 0.05$ significance level when analysed either through each quarter hour or through the whole hour as shown in Table 2. No significant differences occurred during the subsequent tests.

In Trial 2, performance analysed over the whole hour was impaired by triprolidine usually in relation to dose; mean performances in the first and second tests were higher following L(+)-pseudoephedrine 60 mg, but as in the previous study this was not significant. Performance following the combined L(+)-pseudoephedrine (60 mg) and triprolidine (2.5 mg) was always lower than after lactose, differing significantly from that after L(+)-pseudoephedrine alone but not from triprolidine (2.5 mg) alone, on all three tests. Mean performance after all six treatments fell through the hour during all tests and Fig. 2 illustrates performances each quarter hour through the first post-drug test following the individual treatments.

Total confidence scores obtained by arbitrarily giving scores of 3, 2 and 1 to detections rated high, medium or low in confidence usually reflected only the changes in percentage detections, and as a consequence there were no changes in the confidence per correct detection ascribable to treatments. False alarms were infrequent and no changes were ascribable to differences in treatment.

No significant differences ascribable to different treatments occurred in reaction time, digit symbol substitution, or visual search.

Subjective effects

Questionnaire. In answer to the question 'do you think you received an active drug?' subjects recorded either yes, no or don't know. Table 3 shows the number of subjects in the two groups, those recording 'yes' and those recording 'no' or 'doubtful'. The probability of these proportions occurring after any treatment when compared with the proportions following lactose dummy indicate that the two groups of subjects could reliably recognize effects produced by both doses of D(-)-ephedrine and all preparations containing triprolidine (2.5 mg or more). They could not recognize a drug effect from any dose of L(+)-pseudoephedrine in either trial, or the 1.25 mg dose of triprolidine. The results were also analysed more stringently by dividing subjects into two groups defined by correct identification of preparation, i.e. recording a definite 'yes' following drug and a definite 'no' only after lactose, thus excluding from the latter group those who were doubtful. By this method only D(-)-ephedrine (50 mg) was reliably recognized with P values of 0.00614 and 0.04977 at 2.25 and 4.75 h post-drug respectively.

Analogue lines. Relatively few significant differences occurred in Trial 1. Subjects were most tense and most interested following D(-)-ephedrine (50 mg); most relaxed or bored following L(+)-pseudoephedrine (180 mg and 120 mg) respectively; and most sad after lactose. Other dimensions revealed no significant change ascribable to treatments. Significant differences on the various dimensions at 2.25 h and 4.75 h post-treatment for Trial 2 are shown in Table 4. Only dimensions 7 and 10 gave no significant differences. No significant differences occurred at 7.25 h in this trial. In general, the impairment observed in the performance tests by triprolidine is reflected in the subjective assessment. The subjective effects of L(+)-pseudoephedrine (60 mg) are in general ranked at the opposite end of the various dimensions, though differing from lactose only on

Table 3 Replies to question 'Do you think you received an active drug?' by 12 subjects.

Trial 1	Treatment	2.25 h post drug			4.75 h post drug		
		Yes	No and doubtful	P	Yes	No and doubtful	P
		No. of subjects			No. of subjects		
Lactose		1	11		2	10	
D(-)ephedrine (50 mg)		10	2	0.00032	9	3	0.0061
D(-)ephedrine (25 mg)		7	5	0.013	5	7	0.19
L(+)pseudoephedrine (180 mg)		5	7	0.077	3	9	0.5
L(+)pseudoephedrine (120 mg)		2	10	0.5	4	8	0.32
L(+)pseudoephedrine (60 mg)		2	10	0.5	3	9	0.5
Trial 2							
Lactose		2	10		2	10	
Triprolidine (5 mg)		8	4	0.018	9	3	0.0061
Triprolidine (2.5 mg)		7	5	0.045	7	5	0.045
Triprolidine (1.25 mg)		4	8	0.32	6	6	0.097
L(+)pseudoephedrine (60 mg)		2	10	1	2	10	1
Triprolidine (2.5 mg) and L(+)pseudoephedrine (60 mg) combined		8	4	0.018	8	4	0.018

Table 4 Trial 2: Subjective impressions recorded by marking 100 mm lines.

Dimension (left/right)	2.25 h post treatment	4.75 h post treatment
Alert/drowsy	P60 L T1.25 C T2.5 T5	P60 L T1.25 C T5 T2.5
Calm/excited	T5 C T2.5 L T1.25 P60	T2.5 C T5 T1.25 L P60
Strong/feeble	P60 T1.25 L C T2.5 T5	P60 L C T5 T1.25 T2.5
Muzzy/clearheaded	T5 T2.5 T1.25 L C P60	T5 T2.5 T1.25 C L P60
Well co-ordinated/clumsy	P60 L T2.5 T1.25 C T5	P60 C L T1.25 T2.5 T5
Lethargic/energetic	T5 T2.5 C T1.25 L P60	T2.5 T5 T1.25 C L P60
Contented/discontented	P60 T1.25 C T2.5 T5 L	C P60 T1.25 T5 T2.5 L
Troubled/tranquil	T5 L T1.25 P60 C T2.5	L T1.25 T2.5 T5 P60 C
Mentally slow/quickwitted	T5 C T2.5 T1.25 L P60	T2.5 T5 T1.25 C L P60
Tense/relaxed	T1.25 T5 L P60 C T2.5	L T1.25 T5 P60 T2.5 C
Attentive/dreamy	P60 L T1.25 C T2.5 T5	P60 L C T1.25 T2.5 T5
Incompetent/proficient	T5 C T2.5 T1.25 L P60	T5 T1.25 T2.5 C L P60
Happy/sad	P60 C T2.5 L T1.25 T5	P60 C T2.5 T5 T1.25 L
Antagonistic/amicable	T1.25 T5 L T2.5 C P60	T5 L T1.25 T2.5 C P60
Interested/bored	P60 T2.5 L C T1.25 T5	L P60 T2.5 T1.25 C T5
Withdrawn/sociable	T5 T2.5 C T1.25 L P60	T5 T1.25 C L T2.5 P60
Depressed/elated	T5 T1.25 T2.5 C L P60	T2.5 T1.25 L T5 C P60
Self-centred/outwardgoing	T5 C T2.5 T1.25 L P60	T1.25 T5 T2.5 L C P60

Abbreviations used are: L(+)pseudoephedrine (60 mg), P60; triprolidine (1.25, 2.5 and 5.0 mg), T1.25, T2.5 and T5, respectively; combined L(+)pseudoephedrine (60 mg) and triprolidine (2.5 mg), C; lactose dummy, L. The mean scores for 12 subjects following each treatment were ranked in order, and the order is shown for each dimension. Scores following treatments underlined by a common bar did not differ significantly from one another, but differed significantly from all other scores ($P > 0.05$).

alert/drowsy, strong/feeble, muzzy/clear headed, well co-ordinated/clumsy, attentive/dreamy, and happy/sad. From Table 4 it can be seen that the subjective effects following the combination of L(+)-pseudoephedrine (60 mg) and triprolidine (2.5 mg) differ significantly from L(+)-pseudoephedrine (60 mg) alone on 12 dimensions, but from triprolidine (2.5 mg) alone on only one occasion (depressed/elated, at 4.75 h post drug).

Discussion

That the two ephedrine isomers would differ in their relative potency when assessed by cardiovascular changes, was suggested by the work of Patil, Tye & LaPidus (1965) who showed that D(-)-ephedrine was five times more potent than L(+)-pseudoephedrine in producing a pressor response in dogs, while Hughes & Benson (1972) showed that the ratio in man was approximately three to four times and the present study confirms this difference as four to one. Abdallah, Tye, LaPidus & Patil (1967) showed that D(-)-ephedrine released some three times more norepinephrine from rabbit heart than the other three isomers. In general, animal studies by Trevan (1939) and Lanciault & Wolf (1965) suggest that D(-)-ephedrine is considerably more potent in producing central nervous stimulation than L(+)-pseudoephedrine. The present study confirms this in man. In doses approximately equiactive in producing pressor effects, D(-)-ephedrine produced significant increases in tapping rates and in subjective effects enabling the subjects to recognize an active drug, whereas these effects did not occur after L(+)-pseudoephedrine. Stimulant effects, however, were slight, and whilst mean performance in the vigilance test 1.25-2.25 h post-drug was almost always higher than following lactose, the difference was not significant. The sensitivity of this test in detecting a stimulant effect of drugs was established by Bye *et al.* (1973), who showed that the performance of a group of 12 subjects was significantly improved following doses of dexamphetamine (1 and 2.5 mg).

The second trial confirmed the lack of any significant stimulant effect following L(+)-pseudoephedrine, though mean values were higher compared with those following lactose in both the tapping test and the first two vigilance tests. In

addition, scores on the various dimensions of the analogue lines usually indicate a sensation of greater alertness and mental efficiency though again these were not statistically significant. Triprolidine, by contrast, produced significant impairment of both tapping and vigilance tests which was usually related to the dose of drug given. Analysis of the questionnaire showed that subjects could recognize a drug effect from triprolidine (2.5 and 5 mg), and the analogue lines indicated that the 5 mg dose, on all occasions where significant differences occurred, produced the maximum score in the direction of drowsiness and impairment of both mental and physical functions. Impairment of performance in auditory vigilance persisted for up to 7.25 h following all treatments containing triprolidine (2.5 mg or more), but at this time no significant changes in subjective effects occurred, measured either by questionnaire or analogue lines. This suggests that the auditory vigilance test is more sensitive to the central effects of antihistamines of the triprolidine type than subjective effects measured in this manner, and could be used to quantitate drowsiness produced by these drugs.

The effects produced by administration of triprolidine (2.5 mg) and L(+)-pseudoephedrine in combination were usually similar to those of triprolidine (2.5 mg) alone except on the tapping test where the combination produced an intermediate effect. Performance on the auditory vigilance test following the combination never differed significantly from that after triprolidine (2.5 mg), but was different from that after L(+)-pseudoephedrine alone on all three occasions. Similarly, the combination was reliably recognized by subjects as an active drug, similar to triprolidine (2.5 mg) alone, while L(+)-pseudoephedrine alone did not produce a response different from lactose. The analogue lines show that the type of subjective effect produced by the combination must have been similar to triprolidine. It is possible that the site of action of the two compounds in the central nervous system is completely different with triprolidine merely producing a much greater effect. Alternatively it is possible that triprolidine might block the uptake of L(+)-pseudoephedrine into adrenergic neurone terminals thus preventing the effect of this indirectly acting sympathomimetic amine.

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