Comparison of five commonly abused stimulants which are used to reduce fatigue

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ABSTRACT

The effects of five stimulants, which are commonly used by long distance truck drivers, were evaluated to compare their ability to reduce fatigue. The stimulants were caffeine (200 mg), ephedrine hydrochloride (60 mg), pseudoephedrine hydrochloride (60 mg), phentermine (30 mg) and diethylpropion hydrochloride (75 mg). The comparison data were derived from three experiments which were carried out in our laboratory and shared a common methodology (Gibson et al., 1995; Dean et al., 1996 and Springall, 1996). No significant differences in performance were found among the five drug treatments on the 4th hour of a 3-way divided attention task or during a post-testing session (2-way divided attention, digit symbol coding, critical flicker fusion frequency). Systolic blood pressure and oral temperature were not differentially affected by the drugs but a significant (p < 0.01) treatment difference was found for diastolic blood pressure. Pseudoephedrine caused the greatest increase in diastolic blood pressure, when compared with diethylpropion and phentermine. Ephedrine produced the second largest increase, which significantly exceeded that after diethylpropion. Heart rate (HR) was found to be significantly lower after caffeine (p < 0.01) than after ephedrine, pseudoephedrine, phentermine or diethylpropion. Heart rate variability (s.d. of HR) was found to be significantly (p < 0.01) greater after ephedrine than after phentermine or diethylpropion. Caffeine was significantly (p < 0.001) less likely than ephedrine, pseudoephedrine, phentermine or diethylpropion to cause a reduction in the spectral power of the blood pressure component (0.08 - 0.15 Hz) of the cardiac frequency signal. These results suggest that none of the five stimulants, when taken in normal therapeutic doses, differ greatly in their capacity to improve performance and that differences among the drugs are mainly related to their effects on the cardiovascular system.

INTRODUCTION

Fatigue, speeding and alcohol are considered to be the major causal factors in Australian traffic collisions. Not surprisingly, fatigue appears to assume a much greater prominence in crashes.
involving long-distance drivers. In an attempt to delay the onset of fatigue, many long-distance drivers habitually resort to the use of stimulant drugs. Williamson et al. (1992) found that 16.6% of their heavy vehicle driver sample thought that stimulant use was the best way to alleviate fatigue. In other research, 40% to 50% of Australian drivers admitted the use of stimulants, at least on some trips (Linklater, 1977; Hensher et al., 1991; Henderson, 1994).

Stimulants are well known to produce an elevation of mood, a sense of increased energy and alertness, enhanced performance and a decrease in appetite. However, Mehrabian (1986) suggested that when stimulants are used frequently and/or in high doses, they have the paradoxical effect of inducing an emotional undertone of low arousal which is evident in feelings of listlessness, fatigue, lack of ability to concentrate and remain alert, and low energy. In a major collision between a passenger bus and a truck in northern New South Wales in 1989, in which the truck driver and 17 bus passengers were killed, ephedrine-induced hallucination was considered by the Coroner to have been a factor in the collision. Other possibilities included a fatal cardiac arrhythmia or a cerebrovascular accident, both of which could have been expressions of ephedrine toxicity. The driver of the truck was found to have an blood ephedrine concentration which was 80 times the normal therapeutic level.

In a recent study (Bock et al., in press), truck drivers (n = 494), bus drivers (n = 199), long-haul (n = 523) and short-haul motorists (n = 472) were questioned about their experiences of fatigue. Saliva samples were taken from the participants and were analysed for a number of drugs. The incidence of illicit and licit stimulants was much higher in truck drivers than in bus drivers or other motorists. Stimulants detected in the saliva of truck drivers included caffeine (83%), cotinine (18%), ephedrine and pseudoephedrine (8%), phentermine (7%), amphetamine (4%) and methyamphetamime (4%). Diethylpropion could not be assayed and other drugs comprised less than 2%. Hall (1995) reported several studies which investigated the incidence of stimulants and other drugs in truck drivers in the U.S.A. In the first study (Insurance Institute for Highway Safety), illicit stimulants were found in 12% and licit stimulants were found in 5% of drivers. In the second study (National Transportation Safety Board), methyamphetamine and other amphetamines were found in 7% and other stimulants in 8% of fatally-injured truck drivers.

The aim of the present study was to examine whether caffeine and a number of commonly abused stimulants (ephedrine, pseudoephedrine, phentermine and diethylpropion) differed in their ability to reduce fatigue when taken at therapeutic levels. The data were obtained from three experiments (see Table 1 below). Previous research in this area has been limited by a rather narrow focus on cocaine and the amphetamines so that the effects of a large number of closely-related compounds, which are also used to ‘improve’ driver performance, have been largely ignored.
Table 1: Studies included in the analysis.

<table>
<thead>
<tr>
<th>Experiment</th>
<th>Stimulant</th>
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<tr>
<td>1. Gibson et al., 1995</td>
<td>caffeine (200 mg)</td>
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<tr>
<td>2. Dean et al., 1996</td>
<td>ephedrine (60 mg) and pseudoephedrine (60 mg)</td>
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<tr>
<td>3. Springall, 1996</td>
<td>phentermine (30 mg) and diethylpropion (75 mg)</td>
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METHODS

All three experiments used essentially the same methodology. Subjects had to monitor a 4-hour, 3-way divided attention task, which consisted of a central tracking task, a secondary peripheral visual discrimination task and a random visual 'emergency' signal (presented as a red light). An infra-red monitor was clipped to the subjects' ear lobe and heart inter-beat-interval was recorded during the four hours on task. Oral temperature, blood pressure, performance on a short battery of tests (2-way divided attention, digit symbol coding, critical flicker fusion frequency) and subjective estimates of fatigue (sedation, boredom, co-ordination and willingness to drive a motor vehicle) were recorded both before and after the four hour 'fatigue' monitoring task. A full description of the methods is contained in Gibson et al., 1995 and Dean et al., 1996.

Caffeine (200 mg), ephedrine hydrochloride (60 mg) and pseudoephedrine hydrochloride (60 mg) were given to subjects after two hours on task while phentermine (30 mg) and diethylpropion (75 mg) were given at the beginning of the four hour task because they were only available as slow-release formulations. All the studies were placebo-controlled.

RESULTS

Since interest was restricted to between-treatment effects rather than time effects, only data from the 4th hour of the 3-way divided attention task and the post-test battery were analysed because it was expected that any differences between the stimulants would have been at their greatest at this time. A common score (drug minus placebo) was derived and differences between the effects of the drugs were tested by ANOVA.

No significant differences in performance was found among the five stimulant drugs for tracking control ($F_{4,75} = 0.825; p > 0.05$), peripheral detection reaction time ($F_{4,75} = 0.756; p > 0.05$) or 'emergency' reaction time ($F_{4,75} = 0.286; p > 0.05$) on the 4th hour of the 3-way divided attention task. In the post-testing session, tracking control ($F_{4,75} = 0.788; p > 0.05$), peripheral detection reaction time ($F_{4,75} = 0.655; p > 0.05$), digit symbol coding ($F_{4,75} = 0.655$),
1.953; \( p > 0.05 \) and critical flicker fusion frequency (\( F_{4,75} = 1.538; \ p > 0.05 \)) were also not significantly different.

No significant differences in systolic blood pressure (\( F_{4,75} = 1.83 = p > 0.05 \)) or oral temperature (\( F_{4,75} = 1.04; \ P > 0.05 \)) were found among the drug treatments, but there was a significant difference (\( F_{4,75} = 4.11; \ p < 0.01 \)) in diastolic blood pressure. Post-hoc analysis (Newman-Keuls) indicated that pseudoephedrine caused the largest increase in diastolic blood pressure when compared with diethylpropion and phentermine. Ephedrine caused the second largest increase, which was significant when compared with diethylpropion.

Heart rate was found to be significantly lower after caffeine (\( F_{4,75} = 7.52; \ p < 0.01 \)) than after ephedrine, pseudoephedrine, phentermine and diethylpropion. Heart rate variability (s.d. of HR) was also found to be significantly greater after ephedrine (\( F_{4,75} = 4.07; \ p < 0.01 \)) than after phentermine and diethylpropion. Caffeine was found to be significantly (\( F_{4,75} = 17.2; \ p < 0.01 \)) less likely than ephedrine, pseudoephedrine, phentermine and diethylpropion to cause a reduction in the spectral power on the blood pressure component (0.08 - 0.15 Hz) of the cardiac frequency signal.

**DISCUSSION**

We have consistently been able to demonstrate a progressive development of fatigue in placebo groups in this experimental paradigm. A deterioration in performance coupled with an increase in the spectral power of the blood pressure component (0.08 - 0.15 Hz) of the heart rate power spectrum and a slowing of heart rate over time were found. An increase in signal power for the 0.08 - 0.15 Hz frequency band is considered to provide a reliable indicator of fatigue (Mascord & Heath, 1993). When caffeine, ephedrine, pseudoephedrine, phentermine or diethylpropion was administered to subjects, the effects of fatigue were either reversed or stabilised. The results from the current analysis between the individual stimulants suggests that none of the five drugs differ in their capacity to improve performance and that the differences between drugs were mainly related to their cardiovascular effects.

It is commonly believed that caffeine is a stimulant which increases heart rate. In fact, caffeine has complex, varied and often antagonistic effects on the cardiovascular system, depending on the dose and caffeine tolerance of the subject (Myers & Reeves, 1991). In the study by Gibson et al., (1995), caffeine had no significant effect on heart rate. It was found in this study that both heart rate and the spectral power of the blood pressure component (0.08 - 0.15 Hz) were lower after caffeine than after ephedrine, pseudoephedrine, phentermine and diethylpropion.
Ephedrine, pseudoephedrine, phentermine and diethylpropion are all sympathomimetic amines. The principal pharmacological actions of these stimulants on the central nervous system are direct and those on the cardiovascular system are exerted indirectly via catecholamine release from peripheral sympathetic nerves. In therapeutic doses, ephedrine increases blood pressure by increasing cardiac output and causing peripheral vasoconstriction. Tachycardia may also occur. Pseudoephedrine is a stereoisomer of ephedrine with a similar pharmacological profile. Although capable of producing a typical spectrum of sympathomimetic cardiovascular effects, pseudoephedrine is four times less potent than ephedrine (Drew, et al., 1978). The effects of increased sympathetic stimulation induced by phentermine and diethylpropion on the cardiovascular system are manifested as a rise in diastolic blood pressure, palpitations, hypertension and cardiac arrhythmias (Douglas et al., 1983), but such effects normally only occur after supra-therapeutic doses. In this study, it was found that diastolic blood pressure was higher after pseudoephedrine and ephedrine than after phentermine and diethylpropion. The heart rate variability (s.d. of HR) after ephedrine was also greater than for the other stimulants. These results appear to be consistent with current knowledge of the individual stimulant drugs but are of limited predictive value for effects which might occur after large doses taken by tolerant individuals.

REFERENCES


