(12)

Pharmacological Optimization Of Performance: Sleep and Arousal

CPT Vincent M. O'Donnell

Division of Neuropsychiatry

Walter Reed Army Institute of Research

Washington, D.C. 20307-5100

Abstract

Numerous hypnotic (sleep-inducing) drugs are approved and available in the United States. Of these drugs, the benzodiazepine hypnotics appear to be the drugs of choice for military operations due to their relatively minor performance effects as compared to other hypnotic compounds. Important differences exist, however, between the military and civilian applications of these drugs in terms of both efficacy and effects on human performance. Additional research is needed to answer questions raised by these application differences. The initial military use of hypnotic compounds may be most appropriate to long-distance air deployment of troops where there is a reasonable probability that personnel will be able to sleep for six or more hours subsequent to drug administration. Additional military uses for hypnotics may be dependent upon the fielding of a selective counteragent to the hypnotic compound.

Military operations often require that personnel work for several days with little or no sleep. When opportunities for sleep do occur, they are usually quite brief and are not necessarily in synchronization with the individual's normal sleep schedule. Further, the physical and psychological conditions of military operations are far from the dark, quiet, secure, relaxed, and comfortable environment that would promote the rapid onset and maintenance of restful and restorative sleep. Hypnotics, drugs which speed the onset of sleep and help to maintain sleep, are therefore of potential value in military operations.

Because there is a large market for hypnotic drugs in clinical practice (e.g. in cases of insomnia and other types of sleep pathology), there are many approved hypnotic compounds on the market today. Hypnotics available for use in the United States include various anti-histamines and barbiturates, chloral hydrate and chloral betaine, ethchlorvynol, ethinamate, methprylon, and the benzodiazepines. In comparison with the benzodiazepines, the other listed drugs have serious adverse physical and behavioral effects, and some have a very high abuse potential. As a result, the benzodiazepines (e.g. triazolam, temazepam, and flurazepam) have become the most frequently prescribed hypnotics in this country.

Recent military operations have made use of commercially available hypnotics. Israeli forces, for example, administered a commercially available compound to promote

sleep among their troops during the air deployment portion of the Entebbe raid. Temazepam was used successfully by British pilots during the Falklands conflict to enable the best use of irregularly scheduled and infrequent sleep periods under uncomfortable conditions. While the availability of numerous approved hypnotic compounds may encourage their use in military operations, it is important that the substantial differences between military and civilian applications of these drugs be fully understood.

Perhaps the most important of these differences is the greater impact of drug-associated performance decrements on military as opposed to civilian applications. While the benzodiazepines are the class of currently available hypnotics associated with the lowest incidence and magnitude of adverse effects, these effects are still sufficient to cause problems in military operations. The most obvious performance effect of benzodiazepines and other hypnotic compounds is, of course, the induction of sleep. The concomitant reduction in arousal and alertness will affect virtually all types of performance, especially vigilance and sustained attention tasks. In addition, the benzodiazepines have several effects on performance which may differ etiologically from their sleep-inducing effect. These drugs have been demonstrated to impair memory function, especially the consolidation of newly learned material into long-term memory (Clarke, Eccersley, Frisby, and Thornton, 1970; Lister, 1985). A question has been raised as to whether this memory deficit is a primary effect of the drug or whether it is a secondary effect resulting from the drug's hypnotic action--i.e., the drug puts the subject to sleep and in so doing, prevents memory consolidation from occurring (Roehrs, McLenaghan, A., Koshorek, G., Zorick, F., and Roth, 1984). The existence of studies which show memory impairment in subjects who are kept awake after benzodiazepine administration would argue against this theory (Ghoneim and Mewaldt, 1975, 1977). Speed of performance is also consistently slowed by benzodiazepines so that any task involving time pressure (e.g. reaction time, symbol copying) is substantially decremented (Johnson and Chernick, 1982).

Because such effects are of some concern in virtually any population, an effort has been made to select as hypnotics those benzodiazepines which have a relatively short plasma half-life. In civilian use, the chosen hypnotic would hopefully produce a rapid and relatively brief hypnotic effect, during which the subject would refrain from certain critical activities such as driving and the operation of complex machinery. In the military context, the problem is not so simple and the solution not so efficacious.

First, it should be noted that the plasma half-life of a benzodiazepine does not give a particularly strong indication of its onset and duration of actions. While it is true that, in general, the long half-life benzodiazepines have a longer period of action than the very short half-life benzodiazepines, there are some exceptions. Clobazam, for example, is metabolized like a long half-life benzodiazepine, but has a time course of behavioral effects more like a short half-life benzodiazepine. Further, within a given category of benzodiazepines (e.g. short half-life), their is only a loose correlation between half-life and duration of behavioral effects (Hindmarch, Ott, and Roth, 1984).

Next, the duration of behavioral effects is likely to be considerably longer than we would hope for in military operations even with very short-acting benzodiazepines. Triazolam, for example, has a half-life of approximately 3.8 hours. The behavioral effects of a 0.5 mg dose of the drug (a normal clinical dose) have been demonstrated to last at least 6 hours and perhaps as much as 10 hours following administration of the drug (Nicholson and Stone, 1980; Veldkamp, Straw, Metzler, and Demissianos, 1974; Roth, Hartse, Saab, Piccione, and Kramer, 1980). The duration of these behavioral effects is of considerable importance given that there are few situations in military operations when

the users of the hypnotic drug can consistently restrict their activities to those not affected by the hypnotic for such an extended period. Further, the consequences of impaired performance in a military operation are likely to be graver than in a civilian situation. One of the few military situations where personnel have a good chance of remaining inactive for a predictable and extended length of time is in long-distance air deployment, since trans-oceanic flights of six to 10 hours are common.

While the use of hypnotics in such troop deployments would seem appropriate, there are additional considerations. First, the efficacy of benzodiazepine and other hypnotics has not been established under conditions similar to those of military deployment operations. In clinical efficacy studies, an environment is provided which is extremely conducive to sleep, and the drug is administered around the normal sleep time. Contrast this with the environment of the troop transport operation. In daytime operations, the plane may be well-lit and the drug may be administered at a high point in the circadian rhythm. The plane will be noisy and is often quite hot or quite cold. The troops will have a high level of anxiety and autonomic arousal related to their mission, and will be forced to sit upright in crowded conditions for an extended period. While no clinical efficacy studies have come close to duplicating this environment, some facets of it have been studied individually in relation to hypnotic efficacy. Triazolam, for example, has been shown to produce sleep in subjects about to undergo surgery, who probably have high levels of anxiety and autonomic arousal (Keighley, Gannon, Warlow, Jenkins, and Gammon, 1980). The same drug has been demonstrated to induce sleep or drowsiness at times other than night (Seidel, Roth, Roehrs, Zorick, and Dement, 1984; Walsh, Muehlbach, and Schweitzer, 1984) and in subjects who were not kept in typical sleep environments (Gorenstein and Gentil, 1983). There is thus evidence that some hypnotics may be efficacious in the environment of military air deployment operations, but further research is needed.

Because most clinical uses of benzodiazepine hypnotics involve repeated bedtime administrations, there is little available information on possible delayed effects of a single administration. During the minor circadian trough which occurs during the day, a reduction in performance levels typically occurs. This reduction appears to be aggravated by a previous night of benzodiazepine-induced sleep (Hindmarch, et al., 1984). Further, EEG changes at 16.5 to 17.5 hours after administration of a therapeutic dose of triazolam have been demonstrated, well after plasma levels are virtually undetectable (Veldkamp, et al., 1974). What a single administration of a hypnotic at a high point in the circadian rhythm will do to subsequent natural sleep periods is unknown.

The use of benzodiazepine hypnotics in military operations would therefore appear most appropriate to long-distance air deployment of troops. Even when hypnotic use is restricted to such operations, there are questions involving the efficacy and performance effects of hypnotic drug use. While the efficacy question can be resolved by further research, the problems of adverse performance effects may require specific countermeasures. Obviously, it cannot be guaranteed that troops can count on six to eight hours of uninterrupted sleep even during deployment operations. Emergency landings, briefings, assignment changes may all require a high level of alertness and performance. Further, it is the leaders who are most likely to be awakened in the midst of air deployment for changes of plans and decisions. This involves something of a paradox since troop leaders perform the tasks that are most sensitive to sleep deprivation and, at the same time, are the personnel least likely to have adequate time for sleep. Thus the personnel who could most benefit from the use of a hypnotic compound are those who would be most impacted by its performance effects and therefore might be most resistant to its use.

The use of a drug which would specifically counteract the sedating and performance effects of a hypnotic compound could solve these problems by safely awakening personnel and rapidly bringing them to full performance levels. Such a counteragent drug would also expand the potential use of hypnotics. If troops may be rapidly and reliably awakened, then it would not be necessary to restrict the use of hypnotics to occasions when action is not likely to be required for six to eight hours. Ground troops, pilots, and shipboard personnel who will be off duty for only a few hours could use a hypnotic and its counteragent to make optimal use of their rest periods.

This strategy will, however, require a selective counteragent; a general stimulant may awaken the subjects, but will carry with it its own potential for adverse performance effects and may not counter all of the negative effects of the hypnotic. In this respect, the benzodiazepines have an additional advantage over other compounds. While no selective benzodiazepine antagonist has yet received approval for human use in this country, several have been used in experimental studies and hold promise of eventual clinical use (Loew, Nienow, Lawson, Toll, and Uyeno, 1985; Haefely, Bonetti, Burkard, Cumin, Laurent, Mohler, Pieri, Polc, Richards, Schaffner, and Scherschlicht, 1983). On the other hand, many alternate hypnotics such as the barbiturates and ethinamate have either unknown or extremely diverse mechanisms of action, making the development of a selective counteragent unlikely.

In addition to the classes of drugs cited above, experimental work with several endogenous substances such as interleukin-1, delta sleep-inducing peptide, and substance S hold hopes for the future development of hypnotics which may be safer and more efficacious than those currently available (see for example, Wauquier, Gaillard, Monti, and Radulovacki, 1985). As with current compounds, novel hypnotics will need to be evaluated against the unique requirements of military operations and should have a selective and rapidly acting antagonist if they are to receive maximum military application.

REFERENCES

Clarke, P.R.F., Eccersley, P.S., Frisby, J.P., Thornton, J.A. (1970) The amnesic effect of diazepam (Valium). British Journal Of Anesthesiology, 42, 690-697.

Ghoneim, M.M. and Mewaldt, S.P. (1975) Effects of diazepam and scopolamine on storage, retrieval and organizational processes in memory. Psychopharmacologia, 44, 257-262.

Ghoneim, M.M. and Mewaldt, S.P. Studies on human memory: the interactions of diazepam, scopolamine, and physostigmine. (1977) Psychopharmacology, 52, 1-6.

Gorenstein, C. and Gentil, V. (1983). Residual and acute effects of flurazepam and triazolam in normal subjects. Psychopharmacology, 80, 376-379.

Haefely, W., Bonetti, E.P., Burkard, W.P., Cumin, R., Laurent, J.-P., Mohler, H., Pieri, L., Polc, P., Richards, J.G., Schaffner, R. and Scherschlicht, R. (1983) Benzodiazepine antagonists. In E. Costa (Ed.), Benzodiazepines--From Molecular Biology To Clinical Practice, New York: Raven Press, pp. 137-146.

Hindmarch, I., Ott, H., and Roth, T.(Eds.) (1984) Psychopharmacology (Supplementum I). Berlin: Springer-Verlag.

Johnson, L.C. and Chernik, D.A. (1982). Sedative hypnotics and human performance. Psychopharmacology, 76, 101-113.

Keighley, M.R.B., Gannon, M., Warlow, J., Jenkins, C.R.M., and Gammon, R.J. (1980). Evaluation of single-dose hypnotic treatment before elective operation. British Medical Journal, 281, 829-831.

Lister, R.G. (1985) The amnesic action of benzodiazepines in man. Neuroscience and Biobehavioral Review, 9, 87-94.

Loew, G.H., Nienow, J., Lawson, J.A., Toll, L., and Uyeno, E.T. (1985) Theoretical structure-activity studies of beta-carboline analogs, Requirements for benzodiazepine receptor affinity and antagonist activity. Molecular Pharmacology, 28, 17-31.

Nicholson, A.N. and Stone, B.M. (1980). Activity of thehypnotics, flunitrazepam and triazolam, in man. British Journal of Clinical Pharamacology, 9, 187-194.

Roehrs, T., McLenaghan, A., Koshorek, G., Zorick, F., and Roth, T. (1984) Amnesic effects of lormetazepam. Psychopharmacology, 1, 165-172.

Roth, T., Hartse, K.M., Saab, P.G., Piccione, P.M., and Kramer, M. (1980). The effects of flurazepam, lorazepam, and triazolam on sleep and memory. Psychopharmacologica, 70, 231-237.

Seidel, W.F., Roth, T., Roehrs, T., Zorick, F., and Dement, W.C. (1984). Treatment of a 12 hour shift of sleep schedule with benzodiazepines. Science, 224, 1262-1264.

Veldkamp, W., Straw, R.N., Metzler, C.M., and Demissianos, H.V. (1974). Efficacy and residual effect evaluation of a new hypnotic, triazolam. The Journal of Clinical Pharmacology, 14, 102-111.

Walsh, J.K., Muehlbach, M.J. and Schweitzer, P.K. (1984). Acute administration of triazolam for the daytime sleep of rotating shift workers. Sleep, 7, 223-229.

Wauquier, A., Gaillard, J.M., Monti, J.M., Radulovacki, M. (Eds.) (1985) Sleep Neurotransmitters and Neuromodulators. New York: Raven Press.