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INTRODUCTION

Therapeutic drugs acceptable for military aviation are those agents which, without significantly affecting occupational proficiency and safety, may be administered to aviators to alleviate disease which is not itself disqualifying for aviation, or which may allow return to flying status as a result of therapy. This is in contrast to operational medications, pharmacologic agents administered to healthy members to enhance force effectiveness in areas as diverse as vigilance, performance enhancement, Circadian adaptation, and prophylaxis. As a rule, while operational medications may be an issue in any military member, therapeutic agents are of particular concern only in aviation or other high-performance, high-risk occupations, where subtle alterations in psychologic or physiologic performance might have profound effects on performance or safety. For other military members, the standard assessment of clinical efficacy and tolerability which occurs prior to the marketing of a therapeutic agent is usually sufficient for treatment decisions. In the case of operational medications, subtle drug-induced alterations in the aviator are certainly of interest as well, but the relative lack of clinical experience and medical literature means that, as a rule, even the most basic questions of efficacy and safety need to be answered first.

While a large number of medications may be used for treatment of a temporarily grounded aviator, the primary concern here is with therapeutic medications which may be safely employed while the aviator is flying. With the exception of a few over-the-counter drugs which the aviator is specifically allowed to self-administer, medication use by the aviator should be under the direct supervision of the flight surgeon. (This also applies to herbal remedies; drugs derived from botanical sources are no less active for being “natural”, and indeed pharmacotherapy first began with the use of such toxic alkaloids.) Aeromedical supervision is required not only by the disease, which obviously was significant enough to require pharmacotherapy in the first place, but also by the use of the medication, with the attendant risk of early or late toxicity. Follow-up must be based on aeromedical requirements. Clinical indications for surveillance are based on a presumption that patients will self-identify in the case of a symptomatic adverse reaction, and thus surveillance need only be directed at serious side effects which, at least in the early stages, are asymptomatic. In contrast, aviators cannot be presumed to self-identify even with symptomatic side effects, and clinically minor effects, whether symptomatic or not, may have a major impact in the aviation environment.

SELECTION OF DRUGS

Therapeutic Agents

The first consideration to be addressed in selecting therapeutic agents for aeromedical evaluation is whether one could select a class of drugs, or should study individual agents. The former approach is fraught with problems. To begin with, it’s difficult to determine what constitutes a class of medications. Classes are most often based on mode of action, such as receptor blockade. As an example, H₁ antihistamines are generally considered to be a class of medications, yet while the mode of action of these drugs is similar, the incidence of sedation is dramatically different. Calcium antagonists are generally considered a “class”, but the benzothiazepines and diphenylalkylamines cause significant decrease in cardiac inotropy, and are usually considered disqualifying. Chemical similarity might serve as a further class definition, but individual compounds necessarily differ from one another in some fashion. How many side chains or aromatic rings could be substituted, and with what moieties, and still allow a compound to be considered part of a class for aeromedical purposes? Even then, drugs that are chemically similar can be strikingly dissimilar in side effects. Loratadine is
closely related to azatadine, but the former is considered a non-sedating antihistamine, while the latter is a first generation antihistamine which has been used as a verum to induce sedation. Minocycline is in the same “class,” by any accepted definition of that term, as tetracycline and doxycycline, but the vestibular toxicity it causes renders it unacceptable for aeromedical use. Temafloxacin was one of the quinolone antimicrobials, like ciprofloxacin and ofloxacin, yet fatal cases of hypoglycemia caused it to be removed from the market within four months of release. Assumptions about the acceptability of medications based on “class” are generally unwarranted. Drugs for aeromedical use need to be evaluated individually.

The following represents a basic approach for evaluating therapeutic agents intended for chronic use in aircrew.

Licensure
While an aviator with a life-threatening disease is as much a candidate for an investigational new drug as any other clinical patient, such use should preclude flying until the condition has sufficiently resolved and the medication is no longer needed. Therapeutic medications considered for use in an aviator on flying status should be licensed for clinical administration in the aviator’s individual country.

Clinical Efficacy
Disease in the aviator should be treated to the clinical standard of care; the therapeutic agent under consideration should be generally acknowledged to be effective in treatment of the given condition. As a rule, the medication should be shown to be efficacious in the individual aviator before he or she is evaluated for return to the cockpit.

Clinical Experience
While stringent drug testing such as that demanded by national drug licensing agencies requires clinical trials involving several hundred to several thousand subjects, a tremendous amount of additional knowledge about indications, precautions, and adverse effects is gathered in the first several years following a drug’s release. This is principally due to the hundreds of thousands of prescriptions typically written for many drugs in the first years of availability. In addition, use of the medication in less controlled circumstances than that typically found in clinical trials may play a role in eliciting unexpected complications. Sometimes these are serious enough to result in the withdrawal of the drug from the market, such as occurred in the recent past with felbamate and temafloxacin. In short, there is no substitute for experience. Unless there are strong reasons to consider a drug for immediate aeromedical use, it seems most prudent to explore the role of a therapeutic medication in aviation after a reasonable body of clinical experience has accumulated.

Alternatives
Other forms of therapy need to be considered. For example, the small risk of torsades de pointes involved in administering terfenadine to otherwise healthy individuals of aviator age had often been considered a reasonable risk in the past. However, fexofenadine, the active metabolite of terfenadine, does not prolong the QTc interval; when this agent became available, the small chance of arrhythmia with terfenadine appeared to be an unnecessary risk. Nonpharmacologic alternatives should also be explored. For example, omeprazole appears to be a safer drug than originally predicted, since the ECL-cell hyperplasia and the increased risk of gastric carcinoid seen in animal studies have not been observed in human subjects. Nonetheless, many gastroenterologists would consider it unwarranted to commit a healthy young person with chronic gastroesophageal reflux to a lifetime of antisecretory medication, and that surgical correction would be a much preferable option in such an individual.

Potential for Misuse
The potential for misuse or overuse of a medication should be considered. Although the usual clinical concern, i.e., misuse of a mood-altering substance, is an unlikely scenario with respect to waiverable drugs, other situations may arise which are unique to aviation. Certain medical conditions, such as allergic rhinitis, may directly impede the aviator’s ability to fly, and incomplete control of the condition by a medication could prompt the aviator to take a higher dosage. Such an event occurred aboard USS Nimitz. During the investigation of an accident that cost fourteen lives and millions of dollars, the aircraft pilot was found to have a level of brompheniramine eleven times therapeutic level. In this case, of course, the aviator was taking an unapproved medication, but he also significantly overdosed on it in an attempt to control upper respiratory symptoms. While the risk that an aviator may take extra doses of medication is beyond the control of the flight surgeon, whenever
possible the probability of such an event should be taken into account when considering medication to approve for waiver. For instance, an antihistamine that has been shown to be nonsedating across its dosage range is probably a better candidate for therapeutic use than another, otherwise equivalent, agent, which is nonsedating only at lower dosages.

Operational Agents
Guidelines for selecting operational agents are necessarily less clear. While national licensure is preferable, in some cases it may be desirable to begin operational study while the initial research required for licensure is still incomplete. It is also possible that the compound of interest may not be considered to be a drug by all countries (e.g., melatonin). Clinical efficacy and experience may not apply, since in many cases the intended military use has no obvious parallel in civilian medicine. Obviously, alternatives need to be considered, but the operational armamentarium is so restricted that the agent of interest may be under study to provide an alternative to an older, problematic drug. For a number of operational drugs, the potential for misuse is almost intrinsic to the action of the drug, and policies for minimizing that potential are already in place.

AREAS OF CONCERN

Therapeutic Agents
In general, medication effects needing aeromedical evaluation are those that may affect flight performance and safety, yet which are of insufficient clinical importance to have warranted inclusion as part of the original drug studies. Unfortunately, for most medications, effects of aeromedical concern have not been tested as part of these initial trials. Potential areas include systems affecting ability to fly, such as cognition and special senses, and systems affected by unusual aspects of the flight environment, such as physiologic responses to acceleration.

Perhaps the most important potential side effect requiring evaluation is the effect of medications on higher central nervous system function. The critical nature of cognition, alertness, and coordination in the aviator goes without saying; unfortunately, the effects of most medications on these functions has also “gone without saying”, since there is not routinely any attempt at cognitive evaluation during initial clinical trials. It is not enough to rely on self-reporting of symptoms; it is axiomatic that the individual with impaired cognition is often incapable of recognizing such impairment.

Like cognitive processes, information about the impact of a given medication on special senses is rarely available, and proper function of at least some of these systems is critical to aviation. In particular, visual, auditory, and vestibular functions are crucial to successful flying. Impairment of the special senses may, or may not, be recognized by the affected individual.

Cardiovascular effects of drugs are of particular concern in the high-performance aviator, where degradation of acceleration tolerance by a medication which affected vascular tone or sympathetic reflexes could lead to disastrous results. The other cardiac effect of concern is the occasional appearance of arrhythmia, particularly polymorphic ventricular tachycardia, associated with prolongation of the QTc interval.

Besides acceleration stress, other physiologic stresses routinely encountered in aviation include the barometric and hypoxic effects of altitude. While interaction of medication with the former is unlikely, there are at least some theoretic concerns about drugs and hypoxia. A study of first generation antihistamines at altitude suggested a synergistic effect between hypoxia and drug-induced effects on mentation; however, it does not necessarily follow that a nonsedating drug might potentiate the effects of hypoxia. As a separate issue, drugs which affect vascular tone usually affect the pulmonic as well as the systemic vasculature, which could in turn affect hypoxic pulmonary vasoconstriction, and thus perhaps maintenance of arterial saturation. In addition, drugs might disrupt Circadian rhythms, or might affect the organism’s response to temperature or climatic extremes. Evaluating a drug for such specific interactions would be indicated if there were a particular concern about the medication.

Operational Agents
Operational drugs present some unique areas of concern. First and foremost, efficacy in most cases cannot be assumed, and must be established through controlled studies. The absence of central nervous system effects, usually a highly desirable attribute for a therapeutic drug, is a contradiction in terms when applied to stimulants or sedatives; at most, one could hope for a beneficial effect on the targeted neural functions, and a minimal effect on
While the difficulty of evaluating an “aeromedical orphan” via controlled studies is understandable, the loss of even one or two aviators is potentially serious, particularly in an era of fewer aircrew who are more intensively trained in advanced weapon systems. The choices have usually been to either disqualify the individual, use another drug which is established but less suitable (otherwise it presumably would have been used in the first place), or take the chance that a lack of self-reported side effects is adequate for flying safety. An alternative approach for therapeutic medications required by a limited number of aviators is that of an individual occupational evaluation, where the aviator is evaluated before and after starting a drug, in the same way one might perform hepatic or renal function tests before and after beginning drug therapy. Another advantage of such an approach is that it avoids any concerns about a representative sample. There are also certain disadvantages to this approach. For one thing, it only gives information about that individual. Furthermore, it is only possible to explore a null hypothesis; inferences from apparent effects are very limited in the absence of a placebo control. One must evaluate for effects using established tests, previously validated with positive and negative controls, and with enough population norms to interpret individual results. Lastly, one can only obtain answers that have direct relevance to the question of flying status, adhering to an aeromedical/operational standard of care.

METHODS OF EVALUATION

The classic controlled study is usually the method of choice for evaluating medications for efficacy and adverse effects. With the use of placebo (negative) controls, one is able to separate real drug effects from inherent variability in tests or populations, ensuring the validity of positive results. With the use of verum (positive) controls, particularly in CNS testing, one can verify that the test method was capable of detecting a difference, thus supporting the validity of negative results. For operational drugs, such research is, for both practical and ethical reasons, mandatory. The intent with such drugs is to be able to employ them under particular operational conditions and for specific mission requirements; opportunities to preclude adverse effects in those aviators who needed to use the drug would be limited or, in many cases, nonexistent. Thus, advance study is required to define the risk of side effects of aeromedical significance, as well as to establish efficacy.

When applied to evaluation of therapeutic agents for aircrew, the use of the controlled study presents certain negative aspects. First, there is always an assumption that the tested sample represents the treated population; unlike initial clinical trials, however, issues of aeromedical concern do not usually involve more than 20-30 subjects, because they require intensive, time-consuming testing, and because funding is not so readily available. (As a rule, the same limitation of subject numbers applies to operational drug studies.) Second, a drug waiver cannot reasonably be recommended until all areas of concern have been addressed (e.g., cognitive effects, acceleration interaction, etc.), so there is often considerable delay in approving a medication. Lastly, drugs with a limited potential for use, best described as “aeromedical orphans”, would likely never be evaluated through the use of controlled studies; the labor and resources required to properly evaluate a medication would not change regardless of whether the drug would be used by two aviators or two hundred aviators.

others. Concerns about other side effects, such as those involving special senses, do apply to operational drugs, but even there one cannot rule out the possibility of evaluating operational agents for their possible enhancement of such abilities (e.g., the putative effect of bilberry extract on night vision).