Patient-Centric Side Effect Risk Assessment for Medications Used During Aeromedical Evacuations

Shana A. Huntsberger; William P. Butler; Richard R. Chapleau

BACKGROUND: The U.S. Air Force performs more than 6000 aeromedical transport flights annually, both internationally and domestically. Many of these flights include patients requiring pain relief medications. The risk of side effects from such medications administered at altitude is unknown, but understanding these risks is vital when selecting the safest pain management strategies to achieve optimal postflight outcomes.

METHODS: Using an evidence-based medication side effect risk assessment model, we compared our patient-centric approach to an aircrew-centric approach using medications approved for use in U.S. Navy aircrew. We then determined the patient-centric side effect risk of medications commonly used during Air Force aeromedical evacuation (AE).

RESULTS: The patient-centric approach to medication side effect risk assessment demonstrates that the majority of medications currently approved for use during AE have an acceptable side effect risk for the patient (18/22, 82%). Four approved drugs displayed significantly elevated patient risk, with risk scores between 2.0- and 3.2-fold greater than the statistically determined upper allowable ("acceptable") limit and between 1.2- and 2.0-fold above the upper control ("tolerable") limit.

DISCUSSION: Our results suggest that pain management strategies during AE should be tailored individually to minimize the risk associated with pain medications administered en route.

KEYWORDS: patient safety, en route care, aeromedical evacuation pain management, side effects, medication risk assessment.

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The U.S. Air Force's (USAF) aeromedical evacuation (AE) mission is medical care and transport of injured or ill patients from forward operating locations back to specialized facilities for definitive care. Of the 22 medications currently administered during AE flights, 15 of these are pain management medications.[7] A recent study of patients in USAF AE flights found that only 10% of patients experiencing pain above their acceptable threshold were satisfied with their en route pain management[1] and only 48% of patients received some form of relief during transport.[1,2] The precise reasons for lack of adequate pain management are unknown, but the physiological effects of altitude may be contributing factors, as a recent study suggests that explicitly restricting the cabin pressurization results in improved patient outcomes.[3]

While medication action, side effects, and side effect risks are studied generally at ground level by pharmaceutical companies (on average 2500 ft above mean sea level in the United States,[11] depending upon clinical trial locations), the side effect risks of pain medication administered in aircraft at high elevations, possibly under hypobaric and hypoxic conditions, remain mostly unstudied, with a few exceptions. For example, ibuprofen has significantly decreased metabolic turnover, and therefore altered pharmacokinetics and pharmacodynamics, in chronic hypobaric hypoxia.[5] Additionally, using cobalt chloride, a simulant of acute hypoxia, resistance of cancer cells to chemotherapy is permitted by increasing the amount of hypoxia inducible factor-1-alpha protein expression.[12] One hypothesis for the changes in response to therapies may be low blood oxygen saturation, and in short duration commercial flights, mild hypoxemia has been documented.[6]

From the Aeromedical Research Department, U.S. Air Force School of Aerospace Medicine, Wright-Patterson AFB, OH.

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Address correspondence to: Richard R. Chapleau, 2510 Fifth St., Wright Patterson AFB, OH 45433; richard.chapleau.1@us.af.mil.

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Here, we evaluated the potential side effect risks of pain management medications used onboard USAF aircraft using an evidence-based risk assessment model developed for the U.S. Navy (USN) and Army.[10] Taking into account the frequency and severity of every documented side effect for a given drug, the model's conceptual framework treats aviation as a complex system that operates under control theory: a side effect risk score is calculated for each drug and compared within an "allowable-control" chart that was calibrated using medications approved for use in USN aircrew. Validating Prudhomme's supposition that the evidence-based risk assessment model can be readily incorporated into other agencies and fields,[10] we applied this methodology using a patient-centric approach as opposed to an aircrew-centric approach, hoping to gain a better understanding of the parameters affecting patient outcomes following AE transport.

METHODS

In total, 48 drugs were evaluated: 18 medications from earlier work approved for USN aircrew use ("PA"),[10] 20 of 22 approved medications for USAF AE flights [("UA") [other 2 medications already present in "PA" or "PC"],[7] and 10 medications listed as consider/unapproved[10] ("PC").

Side effects and their frequencies were identified for each medication using the following open source and peer-reviewed literature sources:

1. Drugs.com
2. NCBI's PubChem and ToxNet
3. Daily Med
4. Physician's Desk Reference
5. WebMD
6. Leiken and Ploucek's Poisoning and Toxicology Handbook[8]
7. Peer-reviewed sources indexed in Pubmed and/or Google Scholar

As expected from the varied sources of evidence, the incidence of side effects was reported differently between sources. In such cases, we followed the following standardized procedure:

- Ranges within a study were assigned to the highest level of incidence.
- Ranges between studies were assigned to an arithmetic mean.
- When data were reported as "less than" in one source but another source provided a range or percentage, the data from the latter source were used.
- When data were reported in all sources as "less than 1%," the frequency was scored zero as no mean could be calculated (in the case of "less than a small percentage greater than 1%," frequency was scored 1%).
- Studies reporting side effect "equal to or less than placebo" resulted in zero scores.

To maintain consistency with Prudhomme's risk model, we assigned severity multipliers to each side effect using the same four-level categorization.[10] However, the patient-centric focus in our work allowed an expansion of side effect considerations such that the definition of "Subtly Incapacitating" encompasses side effects wherein treatment would be altered and "Totally Incapacitating" becomes those side effects that threaten survival (**Table I**). For example, vertigo may be "Totally Incapacitating" for flying aircrew, but in an immobilized patient, vertigo would only be "Distracting." Additionally, the patient-centric approach scores side effects impacting treatment higher. For example, drugs that thin blood, vasodilate, vasoconstrict, or increase heart rate would all be scored higher, as they will directly influence treatment.

Risk scores were calculated as a sum of the weighted severity score for each side effect. The PA set was rescored and established the model's mean side effect risk score (2182), upper allowable ("acceptable" score) limit (UAL = mean + 1.5 SD; 6345), and upper control ("tolerable" score) limit or maximum tolerable side effect risk (UCL = mean + 3.0 SD: 10,507). Lisinopril and losartan (medications) were excluded from reference calculations; they were serious outliers with a variance 2.35 times the SD of the set mean (risk scores 14,600 and 14,510, respectively). The PC set confirmed that consider/unapproved medications fell within their respective regions of the side effect risk score. Concordance between the two models was determined using Prudhomme's Fig. 2[10] and the scores calculated herein.

Unique side effects with corresponding severity scores, individual risk scores for each medication, and risk assessment calculations for all drugs listed are available as auxiliary material in the electronic edition of this journal (https://doi.org/10.3357/AMHP4748sd.2017). In cases where multiple side effects were provided in a single line with a single frequency, the highest severity score was applied to the group and a single value was given.

RESULTS

Changing the evidence-based risk assessment from aircrew-centric to patient-centric had an overall minor impact on the side effect risk scores identified for the drugs listed by Prudhomme,[10] as 89% are still under the UAL (**Fig. 1**). However, this altered perspective does impact the overall side effect risk scores for individual drugs, as patient-centric scores calculated herein do not correlate well with the aircrew-centric scores (correlation coefficient = 0.468 for the PA set and 0.681 for the PC set). Only lisinopril is above the UAL in both the aircrew-centric and patient-centric models, while in our patient-centric model we found lisinopril, losartan, and simvastatin to be above the UCL. Finally, of the 10 drugs listed as consider/unapproved by Prudhomme (PC set), we found all 10 with side effect risk scores below the UCL. Side effects and risk scores for all drugs can be viewed on line (https://doi.org/10.3357/AMHP4748sd.2017).

The majority (80%) of USAF AE approved drugs (UA) scored well below the UAL (Fig. 1); 50% (10/20) of those drugs scored less than half the mean, and 25% (5/20) scored less than 1/10th the mean. Three of the four drugs exceeding the UAL are opioids (meperidine, morphine, and hydrocodone) and also exceed the UCL, indicating elevated side effect risks to the

Table I. Adverse Effect Severity Score Multiplier Definitions.

ADVERSE MEDICATION EFFECT	AIRCREW-CENTRIC EXAMPLE[8]	PATIENT-CENTRIC EXAMPLE	SEVERITY SCORE MULTIPLIER
Totally Incapacitating	Seizure	Seizure	1000
Subtly Incapacitating	Drowsiness	Vertigo	100
Distracting	GERD	Muscle soreness	10
Mildly Distracting	Dry mouth	Dermal irritation	1
No AE Consequence	Elevated LFT	Elevated LFT	0

GERD = gastroesophageal reflux disease; LFT = liver function test.

patient. As a result, their efficacy must be balanced against their side effect risk when the validating flight surgeon is making pain management decisions. Additionally, the opioid oxycodone (PC) is just below the UCL for the AE patient, but is above the aircrew-centric UCL and unapproved for Navy aircrew use. The fourth drug exceeding the UCL is atenolol, a beta-blocker commonly used in treating hypertension, and it also had the highest side effect risk of all drugs evaluated.

DISCUSSION

Having a standardized, evidence-based method for determining pharmaceutical side effect risk assessment during AE operations provides the community with a rapid capability to respond to new treatment paradigms. Furthermore, it allows for better cross-organization communication, reducing the chance for patient mishaps. By knowing the side effect risks of individual medications, the model can be further adapted to account for combinations of medications and the unique challenges associated with military combat evacuations.[9] Moreover, this model may well offer a foundation for incorporating drug distribution/metabolism/safety predictions from physiology-based pharmacokinetic/pharmacodynamic models as well as the physiological impacts of flight stressors such as altitude, cabin pressure, vibration, and rapid direction changes.[4] Layering pharmaco-predictions and flight physio-impacts upon our side effect risk model could well improve clarity in determining ideal AE treatments.

The side effect risk assessment employed here was a rapid, systematic method. However, a primary limitation of the study is the degree of subjectivity that cannot be standardized that still remains. Categorizing side effects into severity bins is inherently dependent upon both the intended domain of applicability as well as the practitioner's particular level of expertise in the field. It is difficult to postulate a means by which this subjectivity could be completely removed, yet if this were possible, the potential utility of the resulting side effect risk assessments

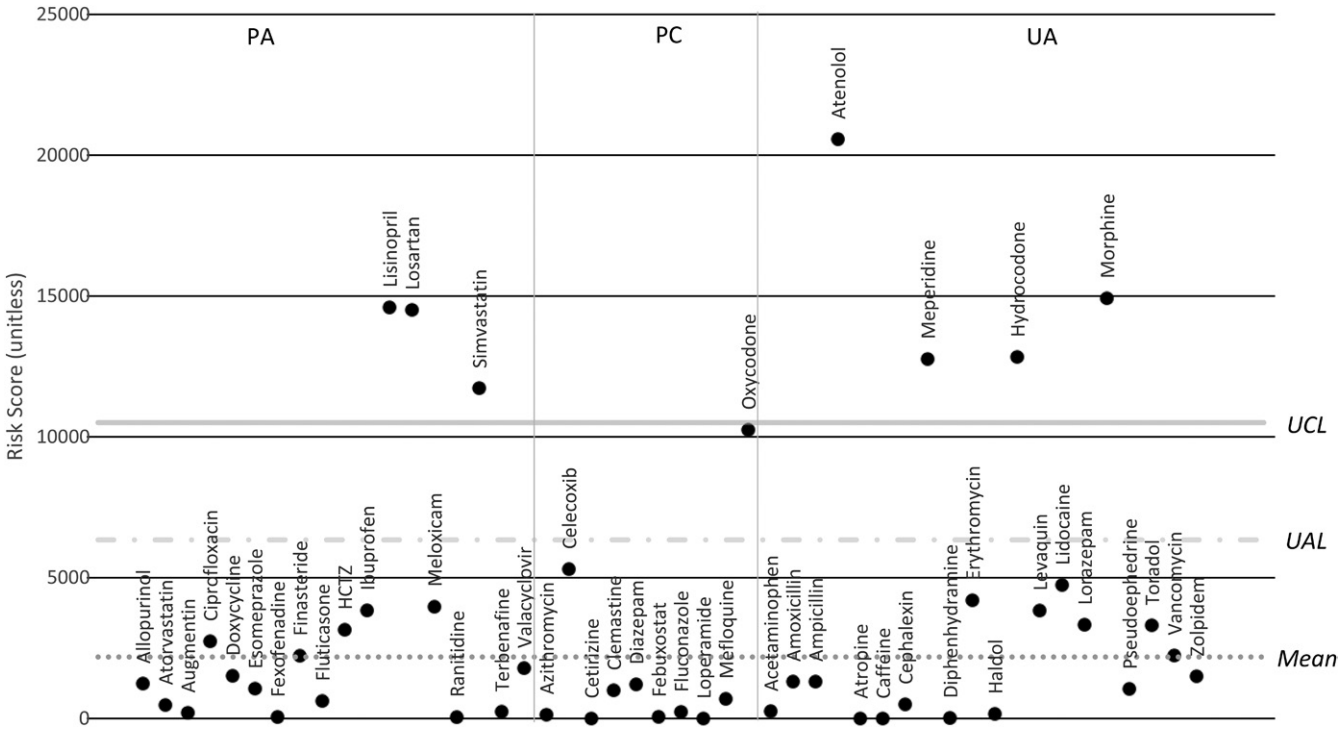

Fig. 1. Patient-centric side effect risk assessments of aeromedically relevant medications. The medications are organized according to the test: Prudhomme approved (PA), Prudhomme consider/unapproved (PC), and USAF AE flight (UA) sets. The mean side effect risk score, UAL, and UCL are shown and were calculated using the PA set.

could be further strengthened. The results presented here are from a theoretical study and the side effects of these drugs at altitude should be evaluated experimentally under hypobaric hypoxic conditions, to provide evidence-based recommendations concerning the effects of aeromedical transport. Such studies would provide significant knowledge of the impacts of flight on patient safety.

To that end, several in vitro and in vivo pilot studies are being performed assessing the integrity of the blood-brain barrier (BBB) at altitude. One in vitro study is investigating more than 40 drugs using a high-throughput parallel artificial membrane permeability assay to determine if common aeromedical evacuation cabin pressures induce BBB changes that would lead to increased drug concentrations in the brain. The aforementioned study is being performed in parallel with an in vivo pilot study where a group of healthy human subjects are being exposed to the same cabin pressure and the amount of a tracer dye inside the brain is measured and compared to an unexposed control group. Once both studies are complete, additional planned studies include developing a physiologically based pharmacokinetic model reflecting brain concentrations of various drugs at altitude and the possible toxicological effects on other organs. Expanding these studies to include additional in vivo studies with healthy subjects or animal models could provide further evidence of increased side effect risks absent controlled studies during actual evacuation flights.

Leveraging an adaptable, standardized side effect risk assessment model,[10] we were able to stratify side effect risk associated with pain medications employed during en route care. This knowledge may enable validating flight surgeons to better prescribe pain medications, permit better inflight pain management by flight nurses and Critical Care Air Transport Teams, and, consequently, reduce the impact of one very important stressor on a patient in an otherwise high stress environment.

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Authors and affiliations: Shana A. Huntsberger, William P. Butler, M.D., and Richard R. Chapleau, Ph.D., Aeromedical Research Department, U.S. Air Force School of Aerospace Medicine, Wright- Patterson AFB, OH; Shauna Huntsberger, Oak Ridge Institute for Science Education, Oak Ridge, TN; and Richard R. Chapleau, Ph.D., Decypher, San Antonio, TX.

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