Drugs and Drug Administration in Extreme Environments

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Emergency medicine must often cope with harsh climates far below freezing point or high temperatures, and sometimes, an alternative to the normal route of drug administration is necessary. Most of this information is not yet published. Therefore, we summarized the information about these topics for most drugs used in medical emergencies by combining literature research with extensive personal communications with the heads of the drug safety departments of the companies producing these drugs. Most drugs can be used after temperature stress of limited duration. Nevertheless, we recommend replacing them at least once per year or after extreme heat. Knowledge about drugs used in extreme environments will be of increasing importance for medical personnel because in an increasingly mobile society, more and more people, and especially elderly—often with individual medical risks—travel to extreme regions such as tropical or arctic regions or to high altitude, and some of them need medical care during these activities. Because of this increasing need to use drugs in harsh climates (tourism, expeditions, peace corps, military, etc) the actual International Congress of Harmonization recommendations should be added with stability tests at +50°C, freezing and oscillating temperatures, and UV exposure to simulate the storage of the drugs at "outdoor conditions."

Introduction and Methods

Drugs are produced for conditions of "civilization," and most of them should be stored and used at 8°C to 25°C. This range reflects the model of kinetic average room temperature.¹⁻⁶ Expiration dates are based on tests of stability within this temperature range over a period of time, at the end of which the amount of active drug must have decreased less than 5%.⁴⁻⁶ In emergency medicine as well as in travel and expedition medicine, these conditions cannot be guaranteed, eg, about twothirds of all rescue operations in the Western Alps take place at temperatures far below 0°C, and often the ampoules are frozen.¹

While some drugs, eg, atropine, lidocaine, and naloxone, are temperature-resistant over an enor-

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mous range $(-20^{\circ}C \text{ to } +70^{\circ}C)$,⁷ others are temperature-sensitive: a pilot study using high-pressure liquid chromatography and infrared spectroscopy showed that some drugs, such as etomidate and clemastine, disintegrated by freezing at -20°C (T. Küpper, 2000, unpublished data). Although it was not investigated whether the substance itself or solvents or stabilizer were disintegrated by freezing, the results prove a significant alteration that creates doubt about whether the drug could be used after cold stress. Such a stress may even be significant under "normal" circumstances. In medical emergency bags, temperatures of up to +80.2°C were measured;³ during transportation on ships, temperatures from -20°C to +40°C occurred;² and in commercial aviation, temperatures from -3.5°C to +42.4°C were measured in medical equipment during flights from Copenhagen to Lagos or Mombasa.8 Castner studied the temperature in drugs stored in helicopters and different types of rescue vehicles. The temperatures varied between

© 2006 International Society of Travel Medicine, 1195-1982 Journal of Travel Medicine, Volume 13, Issue 1, 2006, 35–47 -13.2°C in winter and 50.6°C in summer.⁹ Other investigators have reported similar data.^{10,11} In expedition medicine, temperature stress is even more extreme, with temperatures of less than -50°C during expeditions in the Himalayans or in the polar regions and more than +80°C if the drugs are transported in bags during activities in the Sahara desert.

If it becomes necessary to store or transport drugs for longer distances or time (eg, for trekking, expeditions, military, or peace corps operations), then insulated bags are of limited effect. Within some hours, the internal temperature will be equal to that of the ambient environment. Nevertheless, for short rescue operations, this might be an option. Similarly, carrying the drugs in the inner clothing is not a realistic procedure for longer operations but could be an option for short rescue operations. This is an unrealistic procedure for the general population and for transportation of the whole emergency equipment for a longer distance or time. Transport in the inner clothes should be limited to important and very sensitive drugs, eg, insulin, if the traveler suffers from diabetes. Summarized insulated bags are valuable for specific purposes like urban rescue organizations during winter time but of limited effect during travel in harsh climates.

Extreme temperatures cause degradation of several drugs by chemical reactions like oxygenation, hydrolysis, or decarboxylation.^{12,13} In consequence, the efficacy of the drugs will be decreased, a very important problem for every medical professional (and some educated laymen as well) who are working in remote regions, as travel or expedition doctors. However, literature about this topic is rare, and standard textbooks14,15 provide no or only minimal information.¹⁶ In particular, an actual overview is missing.^{12,13,17,18} Furthermore, only very limited information is available on biological or structural changes in any drug after heat exposure.¹⁶ Valenzuela and colleagues investigated emergency drugs at summer temperatures for a period of 4 weeks.¹⁶ Their major result was that except nitroglycerin, nifedipine, epinephrine, and isoproterenol, the drugs investigated can be used after temperature exposure, which represent a typical summer period in Southwest United States, with temperatures of up to +38°C inside the drug boxes.¹⁶

In addition, most data about drug stability were evaluated by pharmaceutical industry and never published for the medical community. Therefore, we combined a detailed literature research with extensive personal communications with the directors of the departments for drug safety of companies producing drugs used in emergency medicine. Literature search was performed using electronic databases (Medline, DIMDI, and others). Criteria for literature research about thermal resistance were the substances' names in combination with "hot climate," "heat," "high temperature," "temperature resistance," "temperature stability," "thermal disintegration," "thermal degradation," "stability," "desert," "cold climate," "freezing," "arctic," or "high altitude." All papers found were checked for relevance to our topic. A similar approach was used for alternative ways of drug administration (oral, sublingual, intratracheal, buccal).

There is no international consensus on which drugs should be included in an emergency bag. Therefore, we included all drugs recommended in Germany, Switzerland, Austria, France, Netherlands, UK, and Belgium. Discussions with colleagues from the United States, Nepal, and India showed that this combination covers most of the spectrum of emergency drugs of these countries. Unfortunately, the name of some drugs is different in some countries. For better comparison, the generic terms of the drugs described here are given in Tables 1 to 3 for several countries.

Hot climate was defined as exposure at 60°C for several hours. This includes transportation of the drugs inside a car or a backpack during summertime.³ "Cold" was defined by the fact that the ampoule was frozen. The freezing point is an individual constant of each drug and differs over a wide range. While some infusions (eg, polygeline) become gelatinous at some degrees above 0°C, others (eg, methoprolol) freeze at -20°C. No data were available on the freezing point of several drugs. Therefore and because "frozen" and "not frozen" distinguish between "(potentially) usable" and "not usable," we defined cold as frozen.

Furthermore, under extreme climate conditions, it may be impossible to establish an intravenous (IV) line in cases of severe hypothermia or hypovolemic shock, and there are other situations in medical emergencies where this is difficult to do so too. Therefore, we included the possibility of sublingual or oral administration of the ampoules and administration via tracheal tube as alternative procedures of application. If not noted otherwise, the dosage of sublingual or intratracheal administration is the same as the IV dosage. However, it must be pointed out that most information about alternatives of administration is based on case reports and not on state-of-the-art scientific investigations, and therefore, this information must be used with caution.

Netherlands	England	France	Italy	Spain	United States/Canada
Adenosin	Adenosine	Adenosine	Adenosine	Adenosine	Adenosine
Adrenalin	Epinephrine	Epinéphrine	Adrenalina	Adrenalina	Epinephrine
Ajmalin	Ajmaline	Ajmaline	Ajmalina	Ajmalina	Ajmaline
Alteplase	Alteplase	Alteplase	Alteplase	Alteplase	Alteplase
Amiodarone	Amiodarone	Amiodarone	Amiodarona	Amiodarona	Amiodarone
Atropin	Atropine	Atropine	Atropina	Atropina	Atropine
Cafedrin	Cafedrine	Cafédrine	Cafedrina	Cafedrina	Cafedrine
Clonidin	Clonidine	Clonidine	Clonidina	Clonidina	Clonidine
Digoxin	Digoxin	Digoxine	Digoxina	Digoxina	Digoxin
Dextran	Dextran	Dextran	Dextran	Dextran	Dextran
Dihydralazin	Dihydralazine	Dihydralazine	Dihydralazina	Dihydralazina	Dihydralazine
Dobutamin	Dobutamine	Dobutamine	Dobutamina	Dobutamina	Dobutamine
Dopamin	Dopamine	Dopamine	Dopamina	Dopamina	Dopamine
Etilefrin	Etilefrine	Etiléfrine	Etilefrina	Etilefrina	(Ethylefrine)
HES	Hetastarch	Hydroxyéthyl-amidon		_	Hetastarch
Lidocain	Lidocaine	Lidocaïne	Lidocaina	Lidocaina	Lidocaine
Metoprolol	Metoprolol	Metoprolol	Metoprolol	Metoprolol	Metoprolol
Nifedipin	Nifedipine	Nifédipine	Nifedipino	Nifedipino	Nifedipine
Glyceroltrinitrat	Glyceryl trinitrate	Trinitrine	Nitroglicerina	Nitroglicerina	Nitroglycerine/glycery trinitrate
Noradrenalin	Norepinephrine	Norépinephrine	Norepinefrina	Norepinefrina	Norepinephrine
Orciprenalin	Orciprenaline	Orciprénaline	Orciprenalina	Orciprenalina	Orciprenaline
Pindolol	Pindolol	Pindolol	Pindolol	Pindolol	Pindolol
Polygeline	Polygeline	Polygéline	Poligelina	Poligelina	Polygeline
Theodrenalin	Theodrenaline	Theodrénaline	Teodrenalina	Teodrenalina	Theodrenaline
Verapamil	Verapamil	Verapamil	Verapamil	Verapamil	Verapamil

 Table 1
 Generic terms of the drugs effective on the cardiocirculatory system for several countries

HES = hydroxyethyl starch.

Results and Comments

General Principles for Handling of Drugs in Extreme Climate Conditions

If an ampoule was frozen, a visual inspection is a "must" to exclude hairline cracks that could cause contamination or oxidation of the drug.^{11–13,19} But often hairline cracks are not visible to the naked eye. In consequence, ampoules should be replaced after freezing as soon as possible.¹³ Any frozen ampoule should be melted carefully and not by excessive heat. In our opinion, melting frozen ampoules in the mouth, as some colleagues do, is dangerous if they break, and therefore, this should be avoided.

Under any environmental conditions, the ampoule's content should be clear and its color should be as usual. Any drug that contains proteins (eg, insulin) and any emulsion will disintegrate by freezing. The IV administration of frozen emulsions after rewarming is very dangerous because conglomerates of the lipophilic phase may cause embolism of the pulmonary arteries.^{20,21} In consequence, neither emulsions nor protein-containing drugs should be used after exposure to temperatures below +4 to +5°C to exclude freezing (diurnal changes of temperature, etc). Unfortunately, the use of insu-

lated bags is of limited effect on the drug's temperature,⁹ and therefore, drugs must be used with caution in extreme environments even if they are stored in such bags. Capsules (nifedipine, nitroglycerol) are very fragile if they are frozen (R. Blanke, personal communication, 2002), whereas lyophilisates are very temperature resistant if they are not dissolved (T. Herrmann, personal communication, 2002). Exposure of any ampoule to light longer than necessary should be avoided because nifedipine and many other drugs (eg, theophylline, nitroglycerol, and chloralhydrate, insulin as well) show significant sensitivity to UV light.^{12,22}

Data about alternative routes of drug administration proved by clinical or preclinical studies are minimal.^{23,24} If administered by tracheal tube, 5 to 10 mL NaCl 0.9% should be added to the drug, and for some minutes, a moderate hyperventilation should be performed.^{23,25,26} In most cases, the interval between administration and clinical effect will be longer than in IV administration, and it is difficult to estimate the extent of the effect.

Spray and powder applicator systems provide constant dosages even if ambient air pressure decreases, eg, when climbing at high altitude (E. Behse, personal communication, 2003). Sprays are extremely cold-resistant, but they should never

Netherlands	England	France	Italy	Spain	United States/Canada
Alcuroniumchlorid	Alcuronium chloride	Chlorure d' alcuronium	Cloruro de alcuronio	Cloruro de alcuronio	Alcuronium chloride
Buprenorphin	Buprenorphine	Buprénorphine	Buprenorfina	Buprenorfina	Buprenorphine
Clonazepam	Clonazepam	Clonazépam	Clonazepam	Clonazepam	Clonazepam
Diazepam	Diazepam	Diazépam	Diazepam	Diazepam	Diazepam
Etomidat	Etomidate	Etomidate	Etomidato	Etomidato	Etomidate
Fentanyl	Fentanyl	Fentanyl	Fentanilo	Fentanilo	Fentanyl
Haloperidol	Haloperidol	Halopéridol	Haloperidol	Haloperidol	Haloperidol
Ketamin	Ketamine	Kétamine	Ketamina	Ketamina	Ketamine
Metamizol	Metamizol/dipyrone	Métamizole	Metamizol	Metamizol	Metamizol/dipyrone
Midazolam	Midazolam	Midazolam	Midazolam	Midazolam	Midazolam
Morphin	Morphine	Morphine	Morfina	Morfina	Morphine
Naloxon	Naloxone	Naloxone	Naloxona	Naloxona	Naloxone
Pancuronium	Pancuronium	Pancuronium	Pancuronio	Pancuronio	Pancuronium
Pentazocin	Pentazocine	Pentazocine	Pentazocina	Pentazocina	Pentazocine
Pethidin	Pethidine	Péthidine	Petidina	Petidina	Pethidine/ merperidine
Piritramid	Piritramide	Piritramide	Piritramida	Piritramida	Piritramide
Promethazin	Promethazine	Prométhazine	Prometazina	Prometazina	Promethazine
Suxamethonium/ succinylcholin	Suxamethonium/ succinylcholine	Suxaméthonium	Suxametonio	Suxametonio	Suxamethonium/ succinylcholine
Thiopental	Thiopental	Thiopental	Thiopental	Thiopental	Thiopental
Tramadol	Tramadol	Tramadol	Tramadol	Tramadol	Tramadol
Vecuronium	Vecuronium	Vécuronium	Vecuronio	Vecuronio	Vecuronium

 Table 2
 Generic terms of analgesics, narcotics, and psychotropic drugs for several countries

be heated above +50°C because they may explode (K. Issberner, personal communication, 2003). Since fluorinechlorine hydrocarbons were replaced with substances like hydrofluoroalkane as propellants, the dosage of spray applicators does not decrease with lower temperatures.²⁷ Using older systems, the administered dosage was nearly zero at -20°C, whereas it is still constant at this temperature while using new systems.²⁷ The use of powder inhalation systems in humid climate or during rain needs

 Table 3
 Generic terms of other drugs for several countries

Netherlands	England	France	Italy	Spain	United States/ Canada
Acetylsalicylsäure	Aspirin	Acide	Acido	Acido	Aspirin
Butylscopolamin	Hyoscine	acétylsalicylique Hyoscine	acetylsalicylico Hyoscina	acetylsalicylico Hyoscina	(Scopolamine)/
Dutyiseopolailiili	butylbromide	butylbromide	butylbromida	butylbromida	hyoscine
	,		,	,	butylbromide
Clemastin	Clematine	Clémastine	Clemastina	Clemastina	Clemastine
Dexamethason	Dexamethasone	Dexaméthasone	Dexametasona	Dexametasona	Dexamethasone
Dimeticon	Dimethicone	Diméticone	Dimeticona	Dimeticona	Dimethicone
Dimetinden	Dimethindene	Dimétindène	Dimetindeno	Dimetindeno	Dimethindene
Fenoterol	Fenoterol	Fénotérol	Fenoterol	Fenoterol	Fenoterol
Flumazenil	Flumazenil	Flumazénil	Flumazenilo	Flumazenilo	Flumazenil
Furosemid	Furosemide/	Furosémide	Furosemida	Furosemida	Furosemide/
	frusemide				frusemide
Glucose 40%	Dextrose	Dextrose	Dextrosa	Dextrosa	Dextrose
Heparin natrium	Heparin sodium	Héparine sodique	Heparina sodica	Heparina sodica	Heparin sodium
Insulin	Insuline	Insuline	Insulina	Insulina	Insulin
Methylprednisolon	Methylprednisolone	Méthylprednisolone	Metilprednisolona	Metilprednisolona	Methylprednisolone
Metoclopramid	Metoclopramide	Métoclopramide	Metoclopramida	Metoclopramida	Metoclopramide
Neostygmin	Neostigmine	Néostigmine	Neostigmina	Neostigmina	Neostigmine
Physostigmin	Physostigmine	Esérine	Fisostigmina	Fisostigmina	Physostigmine
Prednisolon	Prednisolone	Prédnisolone	Prednisolona	Prednisolona	Prednisolone
Ranitidin	Ranitidine	Ranitidine	Ranitidina	Ranitidina	Ranitidine
Theophyllin	Theophylline	Théophylline	Teofilina	Teofilina	Theophylline
Urapidil	Urapidil	Urapidil	Urapidil	Urapidil	Urapidil

special attention: the devices must be stored dry to avoid agglutination of the powder. For the same reason, the patient may not exhale when using such devices (E. Behse, personal communication, 2003).

Any drug that is stored as lyophilisate or powder, which must be diluted before administration, is very cold-resistant. The heat resistance depends on the substance itself. Although data are sparse, powders like antibiotics and thiopental will be effective when exposed to the environmental conditions described above. For safety, they should be replaced at least once a year when exposed to harsh environmental conditions.

Suppositories may cause problems even when used at the environmental conditions described above. If temperature rises above about 25°C, most suppositories will melt. All substances described below are heat-resistant and will not disintegrate, but it will be impossible to administer them. When the substance cools down inside the package, the "suppository" will have a distorted form, and therefore, it cannot administered as well. After complete melting, often the drug and the wax of the suppository will no longer be homogenous, and the effect will be questionable, even if it should be possible to administer them. At freezing temperature, suppositories show the solidity of glass. They may break into several pieces while unpacking. In any case, they should be rewarmed before unpacking and administration. Those drugs described below as coldresistant should be effective. But it must be pointed out that there are no data about suppositories in extreme environmental conditions.

Drugs

Any metal–organic substance used for disinfection, eg, mercurochrome (merbromine), may disintegrate by freezing. In contrast, products based on alcohol (ethanol–isopropanol mixtures) can be used under any condition (H. Eilbrot, personal communication, 2002).

Emergency drugs for circulation are listed in Table 4. The precipitations found in cold adenosine ampoules will resolve after rewarming. The data about the drug after freezing are limited, but it can be assumed that there is no significant loss.²⁸ When stored at +40°C for 1 year, no degradation was found.²⁸ It must be noted that testing was performed at lower temperatures that are assumed to be critical by us and by others,³ but the drug may be used for a much longer period. Nevertheless, replacement of this not "uncritical" substance once a year is recommended regardless of the date of expiry.

Adrenaline (epinephrine) is not completely robust against heat stress, with a minimal decrease of the substance after 1 year stored at +40°C.²⁹ But the exposure to high temperature was much longer in this study than any storage at these conditions during travel. If stored at +70°C for 3 months, there is no significant degradation.9 Therefore, the loss of efficacy of adrenaline at conditions as described for transportation in cars or backpacks³ is negligible,⁷ although the buffer in which the substance is dissolved shows minor changes that cause higher ionization of epinephrine.¹⁶ There are no data about adrenaline at cold temperatures. The photosensitivity of adrenaline is moderate and does not limit the use of the drug in travel or emergency medicine. A slight opacity of the liquid indicates degradation of the drug.⁹ If administered by tracheal tube, the dosage of adrenaline must be three to five times higher than in IV application (maximum 2–3 mg).²³ Adrenaline as well as atropine administered by tracheal tube shows a depot effect, which lengthens the effect by four times and for lidocaine by two times.²³ Like adenosine, adrenaline ampoules should be replaced once a year regardless of the date of expiry.

Ajmaline is moderately heat-sensitive. Its expiry period will be shorter, and a light yellow color of the liquid indicates degradation.⁹ The drug may be used if stored at +40° for 6 months, but it is recommended that it is replaced once during the summer season.⁹ There are no data available for cold temperatures.

Alteplase should be handled with care and should not be allowed to freeze. Although it is heat-sensitive, it may be used after some hours at +40°C.⁹ At temperatures above +40°C, aggregation of the substance occurs, and the drug's effect will decrease.⁹

Atropine should show some resistance if one takes into account that the berries of deadly nightshade are still toxic after frosty nights. But there are no data about frozen ampoules available (P. Pfleging and N. Jaeger, personal communication, 2002). In contrast, there are data that prove the resistance of atropine against heat stress (P. Pfleging and N. Jaeger, personal communication, 2002). After sublingual application or via tracheal tube, the onset of the drug's effect will be nearly as quick as after IV administration.^{25,26,30,31} But no publication gives any advice about the dosage. Most likely, it is the same as for IV administration. The same can be expected if the ampoule is administered orally, but there are no proven data available.

Data about cafedrine are sparse and do not allow final recommendations to be made. If the liquid shows discoloration, the ampoule should not be used anymore.⁹

Substance	Effective after heat stress	Effective after cold stress	Effective if administered sublingually or buccally	Effective by oral administration of the ampoule's content	Effective if administered by tracheal tube
Adenosine	Yes ²⁸	(Yes) ²⁸	_	_	_
Adrenaline	Yes ⁷	Yes ⁷	No		Yes ^{23,25,26}
Ajmaline			No		No
Alteplase	(Yes) ^{9,16}	No ^{9,16}		_	_
Amiodarone	(= •••) —	Yes	_		_
Atropine	Yes	Yes	Yes ³⁰	(Yes)	Yes ^{25,26,31}
Cafedrine	_	_	_		_
Clonidine	_	Yes	Yes ^{32,33}	_	Yes
Digoxin	_		_	_	_
Dextran	_	_	_	_	_
Dihydralazin	_		_	_	_
Dobutamine	Yes	Yes	_		_
Dopamine	Yes9,16	_	_		_
Etilefrine	_	_	_		_
HES	Yes ⁵²	Yes ⁵²	_		_
Ringer lactate	Yes	Yes	_	_	_
Lidocaine	Yes	Yes	No		Yes
Methyldigoxine	_	_	_		_
Metoprolol	Yes ^{9,16}	Yes ^{9,16}			_
Nifedipine capsules	(Yes)	Yes	No ³⁵	_	No
Nitroglycerol capsules	(Yes)	Yes	Yes	_	—
Noradrenaline	Yes ³⁰		_		_
Orciprenaline	Yes		_	_	_
Pindolol	Yes		_	_	_
Polygeline	Yes	Yes	_	_	_
Theodrenaline	_		_	_	_
Verapamil	Yes	Yes	Yes	_	_

 Table 4
 Drugs for circulation: temperature stress stability and effectiveness by alternative ways of administration

Statements in parentheses indicate argument by analogy if data available do not cover the full range of temperature range assumed for our investigation. Entries in bold indicates that the information is based on personal communication only. —, no data or not indicated. HES = hydroxyethyl starch.

Clonidine ampoules were not investigated on cold resistance yet. Nevertheless, as the preparation is transported frozen during manufacturing, it may be used after cold stress (U. Meyer and H. Bohner, personal communication, 2002), which has been proved for sublingual administration.^{32,33} In contrast, there are no data about its efficacy if given via tracheal tube, but because of its resorption kinetics, normal effects can be expected (U. Meyer and H. Bohner, personal communication, 2002).

Dopamine can be used after storage at 45°C for 6 months.⁹ Therefore, this drug should not be crucial if used in hot environments. There are no data about cold stress.

As a lyophilisate, dobutamine is very temperature resistant, but there are no data when the substance is dissolved (T. Herrmann, personal communication, 2002). Castner reported that the drug showed no degradation after storage at $+70^{\circ}$ C for 6 months.⁹ The drug should not be administered sublingually or endotracheally because then its effect cannot be estimated.

Lidocaine is very temperature-resistant.⁹ If administered via tracheal tube, three times of the normal IV dosage is necessary.^{25,26,31} Up to 10-fold the normal dosage may be needed for children.³⁴

Metoprolol is extremely temperature-resistant. It can be sterilized by autoclave at +121°C and freezes at temperatures below -20°C. After rewarming, the ampoule can be used again.⁹

Nifedipine is not completely stable at temperatures that can be assumed during travel in hot climate because an increasing degradation occurs above 30°C (R. Blanke, personal communication, 2002). Therefore, it should be replaced once a season. At about +35°C to 38°C, physical melting of the drug capsule occurs, and the integrity of the gelatinous material inside is visibly affected by the heat.¹⁶ On the other hand, it is impossible to disintegrate nifedipine by freezing (R. Blanke, personal communication, 2002), but the capsules become extremely fragile. It must be pointed out that, in contrast to widespread recommendations, a sufficient serum concentration cannot be achieved by sublingual administration.³⁵ The patients in those studies that reported any effect after sublingual application were able to swallow, which explains the different results. Theoretically, nifedipine could be administered via tracheal tube, but many problems contradict this possibility: its extreme sensitivity to light, its minimal solubility in water or NaCl 0.9%, and its high affinity to the polyvinylchloride material of the tube—all of them cause enormous problems in dosage (T. Blanke, personal communication, 2002).

Within a short period (some hours) of exposure to heat, nitroglycerol (nitroglycerin) capsules will suffer a complete loss of their active agent because the substance evaporates quickly at temperatures that occur in a car or a backpack at summertime. In consequence, nitroglycerol capsules should be replaced after any heat stress or nitroglycerol spray should be used, which does not evaporate from its bottle. Nitroglycerol sprays can be used after heat stress as it occurs in travel or emergency medicine (see above) without any problems.⁹ After long periods in hot environment (40°C, 26 weeks), small droplets occur in the clear liquid. Then, the bottle should be replaced.⁹ At cold temperatures (below -10°C), small droplets occur near the bottom of the bottle. They redissolve when the bottle will be rewarmed and then the drug can be used again as usual.9

Polygeline infusions, a colloid volume expander, are not completely stable in hot climate as well, but the effect has no clinical consequence except the shortage of the date of expiry—3 years perishable instead of 5 years, (K. Merfort, personal communication, 2002). Using polygeline in cold environments is not feasible as it will begin to gel at about -2°C. There are no data available about its stability after freezing.

Verapamil is temperature-stable. If administered sublingually, 40 to 80 (or to 120) mg should be given and blood pressure should be monitored because a significant decrease is possible even with 40 mg.³⁶⁻⁴¹ It is unclear whether strict sublingual administration can result in therapeutic serum concentrations (see remarks about nifedipine).

Analgesics, narcotics, psychotropic, and related drugs used in emergency medicine are listed in Table 5. Alcuronium is heat-sensitive but may be used after short periods (hours) of temperatures as assumed to be relevant for travel and emergency medicine (see above). Then, it might be necessary to increase the dosage according to the clinical effect.⁹ There are no data available about freezing conditions.

Buprenorphine might be of interest for travel medicine, although there are no data about its temperature resistance. If given sublingually, 0.4 mg show a comparable effect to 10 mg morphine intramuscularly but without any impairment of the respiratory function and the hypoxic ventilatory drive.^{42,43} This may be a special advantage at high altitude.

Although there are no data about the temperature resistance of diazepam as well, the manufacturer characterizes the substance being "not critical," with no significant loss of potency (L. Stoll, personal communication, 2002). There are also no data about the sublingual administration of diazepam, but there is good resorption if it is given via tracheal tube.²³ However, the decision should be taken very carefully because the ethanol– glycol galenics cause significant histopathological damage of the bronchial epithelium.²³ In contrast to adrenaline, atropine, and lidocaine, there is no "depot effect" after application via tracheal tube.²³

Unfortunately, dehydrobenzperidol is no longer being produced. However, many organizations in central Europe placed it into huge stocks for future utilization. Therefore, we included this substance here as well. The period of expiry will be much shorter after heat stress. If stored permanently at +60°C, it will be about 1 month, but this is sufficient for travel medicine if the ampoules are replaced once a year. In general, dehydrobenzperidol should not be used if the ampoule's content appears yellow (B. Steinke, personal communication, 2002). There are no data available about this drug when frozen.

Diazepam is not problematical in travel or emergency medicine. When stored at 30°C for 4 years, there was only 2.4% loss of substance.⁹ Although there are no data, the effect of short exposure to higher temperatures should have limited effect on the efficacy. Preparations with clear liquid contain a special solvent that inhibits freezing.⁹ Diazepam as an emulsion, however, should never be used after freezing because of disintegration of the emulsion. Unfortunately, this effect is often invisible with the unaided eye. If used after disintegration, there is a risk of pulmonary embolism with fatty droplets.⁹ If no IV line can be established, diazepam can be administered rectally very effectively.

The temperature resistance of etomidate is unknown. But the results of our pilot investigation indicate that either the substance itself, the solvent, or the stabilizing substances may disintegrate upon

Substance	Effective after heat stress	Effective after cold stress	Effective if administered sublingually or buccally	Effective by oral administration of the ampoule's content	Effective if administered by tracheal tube
Alcuronium	(Yes) ⁹	_	_	_	_
Buprenorphine	<u> </u>	_	Yes ^{42,43}	Yes ^{42,43}	_
Clonazepam	_	Yes	_	_	_
Diazepam	Yes*	(Yes)16	_	_	(Yes)
Dihydrobenzperidol	Yes	<u> </u>	_	_	<u> </u>
Etomidate	_	No ^{9,*}	_		_
Fentanyl	Yes	(Yes)	_	_	_
Haloperidol	Yes ⁹	_	_		_
Ketamine/ esketamine	Yes ⁹	Yes ⁹	No	Yes ⁴⁴	_
Metamizol	Yes	Yes	No	Yes	Yes
Midazolam	Yes ⁹	Yes	Yes	_	_
Morphine	Yes	_	_	_	_
Naloxone	Yes ^{7,9,16}	Yes ⁹	Yes53-57	Yes ²⁵	Yes
Pancuronium	(Yes) ⁹	No ⁹	_	_	_
Pentazocine	<u> </u>	_	_	_	_
Pethidine	Yes ⁹	_	_		_
Piritramide	No	No	_		_
Promethacine	Yes ⁹	$(No)^9$	_		_
Succamethonium	(Yes)	Yes	_		_
Thiopental	Yes	Yes	_	_	_
Tramadol	Yes	Yes	(Yes)	Yes	(Yes)
Vencuronium	Yes	Yes	—	—	—

Table 5Analgesics, narcotics, psychotropic, and related drugs: temperature stress stability and effectiveness byalternative ways of administration

Statements in parentheses indicate argument by analogy if data available do not cover the full range of temperature range assumed for our investigation. Entries in bold indicates that the information is based on personal communication only. —, no data or not indicated.

*T. Küpper (unpublished data).

freezing (T. Küpper, unpublished data). Castner although giving no details—reports similar findings.⁹ In consequence, etomidate should be used with care in both hot and cold climates.

The knowledge about the cold resistance of fentanyl is limited, but the substance should be relatively stable. If stored at +4°C, there was no degradation (C. Vogt and N. Kubitz, personal communication, 2002). If stored at +50°C, the ampoules should be replaced once a year.⁹ Although theoretically possible, fentanyl solution should not be given orally, sublingually, or via tracheal tube because the monitoring of the dosage will be insufficient.

Haloperidol shows no degradation if stored at +60°C for 3 months.⁹ There are no data available if the drug was frozen.

Ketamine is temperature-resistant: there was degradation neither after storage at +40°C nor after freezing at -15°C.⁹ When administered orally, the bioavailability of the drug is only 16% compared to that in IV administration, but there will be a similar analgesic effect because of the first-pass effect, which modifies the substance to the active

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metabolite, norketamine.⁴⁴ Because of its terrible taste, ketamine should be dissolved in an intensively tasting juice for oral administration (H. Berghof and H. Heinicke, personal communication, 2002). The drug is temperature-resistant: there was neither degradation after storage at +40°C nor after freezing at -15°C.

After storage of midazolam at +30°C, there is no degradation for 3 years.⁹ Although there are no data, there should be no problems if the drug is used in hot environments, but the ampoules should be used or replaced once a year. Freezing does not impair the drug (L. Stoll and H. H. Baetcke, personal communication, 2002). If no IV line can be established, midazolam can be administered rectally very effectively. It can be administered into the nose as well, which is of advantage if children must be treated. The bioavailability is about 50%, but it is immediately effective⁴⁵ as 0.2 mg/kg body weight causes a good sedative effect in 95% of patients within 5 to 10 minutes.⁴⁶ Sometimes patients report a burning feeling in their noses.⁴⁷ Dosages recommended are as follows: for children 0.2 to 0.4 mg/kg and adults 0.1 to 0.2 mg/kg.

There is sparse information about morphine, although it is widely used and recommended in many countries. The drug is heat-resistant at the conditions assumed for our investigation.¹⁶ It should be possible to give the ampoule orally, but there is no detailed information available. One of the authors (T.K.) used 10 mg orally by himself in a survival situation and felt a significant effect after about 5 to 7 minutes, which increased for the next 10 minutes. In any case, the onset of the pain-killing effect will occur later compared to IV administration.

Naloxone can be used after hot and cold stress as assumed by us without any problems.^{7,9} The dosage of naloxone given sublingually, orally, or via tracheal tube is the same as that of IV administration.^{25,31} Given via tube, the onset of its effects is as quick as if the drug was given IV. In contrast to adrenaline, atropine, and lidocaine, there is no depot effect after endobronchial administration.²³

Pancuronium cannot be used once frozen, and its heat resistance is limited.⁹ In hot environments, the ampoules should be replaced at least every 3 months.

There are only few data about pethidine. The substance is stable if stored up to +40°C.⁹ There are no data for cold environments. Anyway, the use of this substance in emergency situations should be considered carefully because of its disadvantages, such as its long-acting toxic metabolites.

Piritramide—although favored by some physicians—is very sensitive if exposed to environmental conditions. Minimal temperature stress causes significant loss of efficacy; thus, the use of the substance should be avoided outside any hospital setting (B. Steinke, personal communication, 2002; C. Vogt and B. Steinke, personal communication, 2002), and opioids should be considered instead.

Promethacine is effective after heat stress as assumed for travel or emergency medicine (see above): if stored at +50°C for 3 months, there is no loss of efficacy. The liquid freezes at 0°C, but—although data are limited—it should be possible to use the ampoule after rewarming.⁹

Suxamethonium (succinylcholine) will not be impaired by cold but by heat. As a consequence, the period of expiry will be shortened. However, no toxic products will occur; therefore, suxamethonium can be used after heat stress as well (G. Kuntz and C. Knoll, personal communication, 2002). The dosage must be adjusted according to the clinical effect. Nevertheless, the ampoules should be replaced at least once a year or after any extensive heat.

A special advantage of tramadol in travel medicine is the fact that it is the strongest pain

killer (except ketamine) of which transport is not limited by international drug regulations (in contrast to morphine and others), and it can be used in hot and cold climate without any problems. In case of oral administration, it should be dissolved in a strongly flavored juice because of its terrible taste. There are no data about the dosage of ampoules given orally, but obviously, the same dosage as recommended for IV application was used in the rare reported cases (A. Anderson-Hillemacher and B. Schwencke, personal communication, 1999). If

drug, nausea will be limited. Other drugs that are often used under emergency conditions but not indicated for circulation or the (central) nervous system are listed in Table 6. Ampoules of acetylsalicylic acid are very cold-resistant, but an increase of free salicylic acid occurs during heat stress. There are no exact data about this degradation, but the long-term stability if stored at +30°C is proven. Therefore, no major problems should occur in travel, expedition, or emergency medicine. As acetylsalicylic acid is a strong acid, it should never be administered via tracheal tube (U. Gessner, personal communication, 2002).

given in fractions or together with an antiemetic

Butylscopolamine is stable at the temperatures assumed to be relevant in travel or emergency medicine.⁹ Compared to IV administration, the drug shows a significantly slower resorption and less pain-killing effect if given sublingually. Therefore, sublingual administration is sufficient in the therapy of less severe spasms (or higher dosages are necessary) but not in severe cases. Given via tracheal tube, the resorption in the tracheal system and efficacy are similar to that in IV administration (D. Telscher, personal communication, 2002).

There are no exact data available about clemastine. In our pilot study, it was stable against freezing at -20°C (T. Küpper, unpublished data), but the ampoules should not be used if the liquid contains crystals after rewarming. If stored up to +40°C, the drug is stable (A. Riebeling, personal communication, 2002). Therefore, short periods of +60°C as assumed in our survey for travel medicine should not cause significant degradation. In contrast, dexamethasone is less heat-resistant and should be replaced once a summer season or after severe heat stress (E. Kraus, personal communication, 2002).

Dimeticon (poly(dimethylsiloxan)) tolerates temperatures very well. After storage at +45°C for 6 months or after freezing, there was no degradation.⁹ Because of its comparable chemistry, the same should be true for simethicone, a polysilyene derivate, although we could not get or find any data.

Substance	Effective after heat stress	Effective after cold stress	Effective if administered sublingually or buccally	Effective by oral administration of the ampoule's content	Effective if administered by tube
Acetylsalicylic acid	Yes	Yes	No	Yes	No
Butylscopolamine	Yes	Yes	Yes	Yes	Yes
Clemastine	(Yes)	(Yes)	_	_	_
Dexamethasone	(Yes) ¹⁶	Yes	Yes	Yes	_
Dimeticon	Yes ⁵	Yes ⁹	_	Yes ⁹	_
Dimetinden	—	—	—	—	—
Fenoterol spray	Yes ⁷	Yes ⁷	No	_	Yes
Fenoterol ampoules	—	—	—	—	—
Flumazenil	—	Yes	_	_	—
Furosemide	Yes ¹⁶	Yes ¹⁶	_	_	Yes ¹⁶
Glucose 40%	Yes	Yes	(Yes)	Yes	(Yes)
Heparin	(Yes) ⁹	(No)	_	_	_
Insulin	(Yes)	No	_	_	_
Methylprednisolone	Yes ⁹	No ⁹	_	_	_
Metoclopramide	Yes	_	(Yes)	Yes	_
Physostigmin	_	No	No	_	No
Prednisolone	Yes	Yes	Yes	_	_
Prostigmine	_	(Yes)	No	_	No
Ranitidine	(Yes)	Yes	No	_	No
Theophylline	Yes	_	_	_	_
Urapidil	Yes	Yes	(Yes)	_	(Yes)

Table 6 Other drugs used in emergency medicine: temperature stress stability and effectiveness by alternativeways of administration

Statements in parentheses indicate argument by analogy if data available do not cover the full range of temperature range assumed for our investigation. Entries in bold indicates that the information is based on personal communication only. —, no data or not indicated.

Fenoterol spray shows good resorption if given via tracheal tube, but a special connector is necessary (eg, tube inhaler, VBM Medizintechnik, Suls a.N., Germany) as well as 3 times the normal dosage^{25,26,31} and up to 10 times for children.³⁴ Probably this effect is caused by adherence of the drug to the tracheal tube's surface.

Like clemastine, there are only data indicating stability at +40°C for furosemide, but short exposure to +60°C should be without significant degradation of the drug. If given via tracheal tube, the resorption is similar to the slower oral kinetics (W. Lippke, personal communication, 2002). When frozen, furosemide forms linear crystals that cannot be redissolved by heating. This limits the use of this drug to warmer conditions.

Heparin is more heat-resistant than expected by most physicians: if stored at +40°C for 6 months, there is no effect on its efficacy.⁹ For freezing temperatures, there are no data available, but in cold environments, the drug should be handled with care because degradation has to be expected. This includes low-molecular heparins. Here the advice "never freeze it" is included in the package information leaflet (eg, enoxaparin).

Insulin should be used as soon as possible if exposed to heat stress of +60°C and, of course, while

monitoring its effect on blood glucose concentration. Otherwise, it should be replaced because the period of expiry will be reduced by heat. Of course, insulin being a protein will denaturate by freezing, and it is moderately sensitive to UV light as well.²² Therefore, in cold climates, it should be carried in a nonbreakable case inside the jacket together with the blood glucose test device. Blood glucose measurements with these devices result in underestimation if the system is colder than +14°C because the procedure is based on a temperature-dependent chemical reaction.²² Any testing with equipment colder than 0°C is impossible.²²

Methylprednisolone shows no degradation if stored at +60°C for 12 months. During production, it freezes at -40°C without any impact on its efficacy.⁹ Thus, it should be possible to use the drug in cold environment, although there are no data available.

Metoclopramide must be stored in darkness. Therefore, the box with the ampoules should be only opened if definitely necessary, especially in climates with high UV radiation. In hot environments, the drug can be used because there is no degradation after storage at +50°C for 3 months. After freezing, it can be used as usual as well.⁹ The data about sublingual administration are limited (R. Halla and K. Pirilis, personal communication, 2002).

Prednisolone is temperature-resistant. Sublingual application results in 3 times the IV dosage for adults^{25,26,31} and up to 10 times the dosage for children.³⁴ The data about cold resistance of prostigmine and those of heat stability of ranitidine are limited (L. Nelles, personal communication, 2002). But the characteristics at high temperature are similar to those of furosemide (see above), and therefore, no problems should appear in travel medicine (T. Reblin, personal communication, 2002).

There are no data also about theophylline ampoules if given sublingually, but it is possible to drink one to two ampoules (D. Bauer and T. Klees, personal communication, 2002). This may be of special advantage if the drug is used to prevent acute mountain sickness at high altitudes.⁴⁸ Because of the terrible taste, theophylline ampoules should be diluted with water before drinking or given together with a strongly flavored juice.

Urapidil, a peripheral α -blocker like prazosine, is not completely stable at +60°C and should be replaced at least once a summer season or after a prolonged heatstress. It can be used in cold environment without problems. The ampoules should also be replaced if the liquid appears yellow or pink, which indicates degradation. Data about sublingual or intratracheal administration are limited, but the quick and complete resorption of the drug by the mucous membrane has been demonstrated. Therefore, it should be possible to achieve therapeutic serum concentrations. But it may be difficult to anticipate the effect of blood pressure decrease (R. Schneider and T. Wolffgram, personal communication, 2002).

Conclusions

Most drugs can be used after temperature stress of limited duration. It should be recommended that they are replaced at least once per year or after exposure to extreme heat. Those drugs indicated as temperature-sensitive (cf. Table 1–3) should be replaced after any temperature stress beyond the limits given by the manufacturers (in most cases 25°C). The expiry periods of drugs, evaluated according to International Congress of Harmonization recommendations,^{49,50} are of limited value for travel, expedition, and emergency medicine. Like others,²⁹ we suggest the inclusion of stability tests at +50°C, freezing and oscillating temperatures, and UV exposure in the postregistration procedure to simulate the storage of the ampoules under "outdoor" conditions. For existing drugs used in emergency medicine, research about these topics is necessary to increase safety. Actually, no data are available, eg, for amiodarone, diphenhydrinate, ketorolac, norepinephrine, ondansetron, prochlorperazine, salbutamol, and others.

Again it must be pointed out that any drug must be used with caution in extreme environmental conditions and that alternative procedures of administration are a "last-chance decision" if normal administration should be impossible. If used by alternative administration, the effect of the drug must be monitored carefully because its pharmacokinetic properties will differ from those at normal administration. More investigations are necessary to improve drug safety in extreme environments, especially for hypobaric hypoxia at high altitude. There are several reports about unexpected effects of drugs when used at high altitude, mostly of increased efficacy. Although hypobaric hypoxia may explain the intensified efficacy of any sedative drug, other effects cannot be explained by hypoxia alone, eg, the hypotensive effect of nitroglycerine, which is sometimes extreme at altitude even at low doses (T. Küpper, unpublished observations). A combination of several effects of altitude, such as lower blood volume caused by high-altitude diuresis, may cause this adverse reaction, which cannot be investigated in simple hypoxic conditions but in altitude laboratories only. In addition, there is only sparse information about drug effects in hypothermic patients. Increased protein binding and decreased resorption (except in the case of IV administration) causes decreased effectiveness. Thus, further investigations are necessary to increase safety of emergency medicine in the field.

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Declaration of Interests

The authors state they have no conflicts of interest.

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