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CONSENSUS STATEMENT

OF THE

UIAA MEDICAL COMMISSION

VOL: 10

The Effect of Extremes of Temperature on Drugs

With notes on side effects and use of some other drugs in the mountains

Intended for Doctors, non-medical persons and Trekking / Expedition Operators

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2008

Basic problems of drug use in the mountains

Harsh environmental factors – especially heat and cold – can significantly affect drugs, the substances as well as stabilisers, solvents etc. Temperatures inside emergency medical bags have been reported to be between -40°C and +80°C. Such temperature extremes may be even harsher in a mountaineering environment. The following recommendations are given to handle drugs under such circumstances (for details see [1]):

- If an ampoule was frozen, a visual inspection is a “must” to exclude hairline cracks that could cause contamination or oxidation of the drug.
    - **Note:** often hairline cracks develop and are not visible to the naked eye Therefore previously frozen ampoules should be replaced as soon as possible.
- Any frozen ampoule should be melted carefully and not by excessive heat.
    - Melting frozen ampoules in the mouth is dangerous! If they break, it may result in the person ingesting the drug and having their mouth cut!
- Under any environmental conditions, the ampoule’s content should be clear and its colour should be as usual.
- Any drug that contains proteins (e.g. insulin) and any emulsion will disintegrate by freezing. Never use it then, lethal outcome by pulmonary embolism may be the consequence!
- Capsules (e.g. nifedipine, nitroglycerol) are very fragile if they are frozen, whereas lyophilisates are very temperature resistant if they are not dissolved.
- Avoid exposure of any ampoule to light longer than necessary because many drugs (e.g. nifedipine, theophylline, nitroglycerol, chloralhydrate, insulin) show significant sensitivity to UV light.
- Spray and powder applicator systems provide constant dosages even if ambient air pressure decreases, e.g., when climbing at high altitude. Sprays are extremely cold-resistant, but may explode if heated above +50°C.
- Powder inhalation systems must kept dry in humid climate or during rain to avoid agglutination of the powder. For the same reason, the patient should not exhale into such devices.
- Suppositories will melt above about 25°C. At freezing temperature they show the solidity of glass. They may break while unpacking or cause injuries during application. In any case, they should be re-warmed before unpacking and administration.

Use of emergency drugs in the mountains

Tables 1-3 give an overview about the topic. In these tables “heat exposure” means exposure to +60°C for several hours. “Cold exposure” was defined by the fact that the ampoule was frozen. For details see [1]. It must be pointed out, that the knowledge of drugs in extreme environment is limited. Use them with caution in any case!

A special problem is the use of narcotics. The medical societies leave no doubt, that strong painkillers as morphine are a “must” for any emergency kit of a physician going to the mountains. But for some strong painkillers (especially morphine or their derivatives) there are restrictions for transport and especially international border crossing, even inside the European Community! Inform yourself about the actual regulations at the local authorities of your country and of the country of destination well before departure. Or alternatively: use tramadol and ketamine, as these drugs are not restricted in any country.

Substance	Effective after heat exposure	Effective after cold exposure	Effective if administered sublingually	Effective if administered by tracheal tube
Adenosine	Yes	Yes	--	--
Adrenaline	Yes	Yes	No	Yes[1, 2]
Ajmaline	Yes	--	No	No
Alteplase	Yes	--	No	No
Amiodarone	--	Yes	--	--
Atropine	Yes	Yes	Yes	Yes[3]
Cafedrine	--	--	--	--
Clonidine	No	Yes	Yes	Yes
Digitoxin	--	--	--	--
Dextran	--	--	--	--
Dihydralazin	--	--	--	--
Dobutamine	Yes	Yes	--	--
Dopamine	Yes	--	--	--
Etilefrine	--	--	--	--
Hydroxyethyl starch	Yes	Yes	--	--
Ringer lactate	Yes	Yes	--	--
Lidocaine	Yes	Yes	No	Yes[4]
Metyldigoxine	--	--	--	--
Metoprolol	Yes	Yes	--	--
Nifedipine capsules	Yes[5]	Yes	No	No
Nitroglycerol capsules	Yes[6]	Yes	No	--
Noradrenaline	Yes	--	--	--
Orciprenaline	Yes	--	--	--
Pindolol	Yes	--	--	--
Polygeline	Yes	Yes[7]	--	--
Theodrenaline	--	--	--	--
Verapamil	Yes	Yes	Yes[8]	--

Table 1: Drugs for circulation, no data or no indication; detailed discussion in [1]

[1] „Depot effect"! Effect will be lengthened by four times.
[2] 3-5 times of normal dosage necessary
[3] „Depot effect"! Effect will be lengthened by four times. No dosage given in literature. Use standard dosage and monitor patient.
[4] Adults need 3 times of normal dosage (children up to 10 times). "Depot effect" doubles the length of the effect
[5] Increasing disintegration above 30°C. Replace after heat stress, but at least after season.
[6] Total loss of substance (vaporization) after short periods (hours!) >40°C. Replace after any heat stress.
[7] Coagulates below +4°C. Keep warm, especially the canula and the infusion system!
[8] Dosage: 40-80 (-120) mg; decrease of blood pressure possible, monitor patient!

Substance	Effective after heat exposure	Effective after cold exposure	Effective if administered sublingually	Effective if administered by tracheal tube
Alcuronium	Yes	--	No	No
Buphenorphine	--	--	Yes[9]	--
Clonazepam	--	Yes	--	--
Diazepam	Yes	Yes	No[10]	Yes
Dihydrobenperidol	Yes	--	--	--
Etomidate	--	--	--	--
Fentanyl	Yes	Yes	No	No
Haloperidol	Yes	--	--	--
(es)Ketamine	Yes	Yes	No[10]	No
Metamizol	Yes	Yes	No[11]	Yes
Midazolam	Yes	Yes	Yes	--
Morphine	Yes	--	No[12]	--
Naloxone	Yes	Yes	Yes	Yes
Pancuronium	Yes[13]	No	No	No
Pentazocine	--	--	--	--
Pethidine	Yes	--	--	--
Piritramide	No	No	--	--
Promethacine	Yes	Yes	--	--
Succamethonium	Yes[13]	Yes	--	--
Thiopental	Yes	Yes	--	--
Tramadol	Yes	Yes	Yes	Yes
Vencuronium	Yes	Yes	--	--

Table 2: Analgesics, narcotics, psychotropic, and related drugs
(-- no data or no indication; detailed discussion in [1])

[9] 0.4 mg orally administered show an effect similar to 10 mg morphine, but the hypoxic ventilatory drive will not be impaired!
[10] Oral administration possible (similar dosage than i.v.)
[11] Oral and rectal administration possible, similar dosage tan i.v.
[12] Oral administration possible. No data about dosage in literature. In most cases similar dosage than for i.v. administration is used. Monitor patient for sufficient breathing, especially at altitude!
[13] (relatively) temperature sensitive. Replace at least every 3 month or after heat stress.

Substance	Effective after heat exposure	Effective after cold exposure	Effective if administered sublingually	Effective if administered by tracheal tube
Antibiotics	--	--	No	No
Acetylsalicylic acid	Yes	Yes	No[14]	No[15]
Butylscopolamine	Yes	Yes	Yes[16]	Yes
Clemastine	Yes	Yes	--	--
Dexamethasone	Yes[17]	Yes	Yes	--
Dimeticon	Yes	--	No	No
Dimetinden	--	--	--	--
Fenoterol spray	Yes	Yes	No	Yes[18]
Fenoterol ampoules	--	--	--	--
Flumazenil	--	Yes	--	--
Furosemide	Yes	No[19]	--	Yes
Glukose 40%	Yes	Yes	Yes[14]	Yes
Heparin	Yes	--	No	No
Insulin	Yes[20]	No	--	--
Methylprednisolone	Yes	Yes	--[14]	--
Metoclopramide	Yes[21]	Yes	Yes	--
Physostigmin	--	No	No	No
Prednisolone	Yes	Yes	Yes[22]	--
Ranitidine	Yes	Yes	No	No
Theophylline	Yes[21]	--	No[14]	No
Urapidil	Yes[17, 23]	Yes	Yes	Yes

Table 3: Other drugs
(--: no data or no indication; detailed discussion in [1])

[14] Oral application (drinking) of the ampoule is possible
[15] Never! Life-threatening pneumonia may arise!
[16] Effect reduced, higher dosage necessary, but no dosage listed in literature. Monitor patient!
[17] Not complete stable. Replace once a season if transported at about >30°C.
[18] With connector only (e.g. Tube Inhaler), use 3-times the dosage for adults, up to 10-times for children.
[19] Limited cold resistance: Can be used in cold environment, but after freezing there are crystals which do not resolve again and the ampoule should not be used.
[20] Expiration period will be shortened. Use combined with blood sugar control and replace as soon as possible.
[21] Keep dark! The substance is very UV sensitive.
[22] Adults: 3-times of normal dosage, children up to 10-times.
[23] Do not use if ampoule's content changes colour to a yellowish or pink.

Side effects of special importance at altitude

Again, the knowledge is limited. The following list of drugs, possible problems and consequences when using them in the mountains is preliminary!

Substance (group of…)	Possible problem at altitude	Consequence(s)/risk in alpine environment or at high altitude
Nifedipine capsules	Capsules (not slow release!) may cause severe decrease of blood pressure and collapse?	Use only for sitting or lying patients. Secure patient, avoid falls! Shock position for some minutes in case of severe symptoms. Better not to use at all.
Nitroglycerol	Drastical decrease and collapse possible even when small dosages were applied	Use only for sitting or lying patients. Secure patient, avoid falls! Shock position for some minutes in case of severe symptoms.
Benzodiazepines	Decreased ventilation compared to sea level.	At altitude the indication for benzodiazepines is rare (except for anaesthesia). If necessary, prefer short-acting ones (e.g. temazepam)
Antihypertensive drugs	Increased effect at altitude may result in orthostatic problems.	It may be necessary to reduce antihypertensive therapy at altitude, especially diuretics (dehydrated persons!).
Ergot alkaloids	Increased risk of frostbite!	Avoid these drugs for mountaineers!
Vascular dilatators	Increased risk for hypothermia and orthostatic problems	Take special care to keep patient warm!
Acetyl salicylic acid	Increased risk for haemorrhages!	Not to be used in mountaineering!
Antidepressants	Reduced self-assessment, critical facility and power of concentration; risk of overestimation of one's own capabilities	Take care! Increased risk of (severe) accidents!
Tranquiliser	Alertness and ability to respond is reduced (add to the independent effects of hypoxia!)	Take care! Increased risk for (severe) accidents!
Tetracyclines	Increased risk for phototoxic reactions	
Corticoides	Euphoria, reduced self-assessment, reduced risk awareness, stress intolerance	Take care! Increased risk for (severe) accidents! (and if something happens, there is reduced stress tolerance…)
Strong painkillers	Added effect with hypoxia: severe respiratory depression, significant reduction of power of concentration, alertness, and ability to respond	Take care! Increased risk for (severe) accidents!

Table 4: Important side effects of drugs at altitude [2]

Other drug related matters in the mountains

Drugs for the treatment of mountain illnesses, including acute mountain sickness, high altitude cerebral and pulmonary edema, are considered in UIAA MedCom recommendation No. 2. The use of acetazolamide (Diamox) as prophylaxis for AMS is controversial, and is considered in other recommendations (no.2 and some others, which are in preparation).

Heparin is under discussion to avoid high altitude related thrombosis and pulmonary embolism. At present there are not sufficient data to recommend this strategy. It must be taken into account, that the handling and storage of heparin is critical at high altitude as the risk of bleeding increases.

Acetyl salicylic acid is as well in discussion to prevent altitude related thrombosis and pulmonary embolism. UIAA MedCom definitely does not recommend the use of this substance at high altitude for several reasons. First of all, there are no data which prove a sufficient effect. The mechanism is thrombocyte coating. This effect decreases cellular coagulation in the arterial part of the circulatory system, but not the acellular system which is most important in the venous system. Otherwise there are data of a significant increased risk for haemorrhages (retina, gastrointestinal tract).

For **contraceptive drugs** see UIAA MedCom Consensus Statement No. 12 “Women at altitude”.

Phosphodiesterase inhibitors (Sildenafil, Tardalafil, Vardenafil etc.) are in discussion to treat HAPE. Although it is expected that these substances may be effective to threat HAPE, UIAA MedCom does not recommend them at present. Data are scarce and significant side effects which are of special importance at high altitude are well known (e.g. massive headache).

NSAIDs do not prevent muscle damage by extreme exertion, although many athletes think so [3]. In some cases acute renal failure has been reported after exercise and NSAIDs. These observations were done at low altitude, but high altitude and dehydration may be additional risk factors. Of course the danger of bleeding (gastric ulcer) is well known and may be increased by hypoxic environment. UIAA MedCom recommends to restrict the use of NSAIDs as much as possible, especially for acetyl salicylic acid (see above) and diclofenac.

References

1. Kupper T, Schraut B, Rieke B, Schoffl V, Steffgen J. Drugs and drug administration in extreme climates. J Travel Med 2006;13:35-47
2. Kupper T. Tourenapotheke für den Bergsteiger und den bergsteigenden Arzt [Medical kit for mountaineers and mountaineering physicians]. In: Berghold F ed, Lehrskriptum Alpin- & Höhenmedizin. 4th edition ed. Innsbruck: Austrian Society for Alpine and High Altitude Medicine; 2002:105-120
3. Nieman DC, Henson DA, Dumke CL, et al. Ibuprofen use, endotoxemia, inflammation, and plasma cytokines during ultramarathon competition. Brain Behav Immun 2006;20:578-584

Appendix 1: Generic terms of the drugs for several countries

Germany	U.K.	France	Italy	Spain	USA
Adenosin	Adenosine	Adenosine	Adenosine	Adenosine	Adenosine
Adrenalin	Epinephrine / Adrenaline	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	Etilefrine
Hydroxyethyl-Stärke (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	Glyceryl trinitrate
Noradrenalin	Norepinephrine / Noradrenaline	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 5: Cardiocirculatory system

Germany	U.K.	France	Italy	Spain	USA
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 6: Analgesics, narcotics, and psychotropic drugs

Germany	U.K.	France	Italy	Spain	USA
Acetylsalicylsäure	Aspirin	Acide acétylsalicylique	Acido acetylsalicylico	Acido acetylsalicylico	Aspirin
Butylscopolamin	Hyoscine butylbromide	Hyoscine butylbromide	Hyoscina butylbromida	Hyoscina 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 / Frusemide	Furosémide	Furosemida	Furosemida	Furosemide / Frusemide
Glucose 40%	Dextrose	Dextrose	Dextrosa	Dextrosa	Dextrose
Heparin Natrium	Heparine sodium	Héparine sodique	Heparina sodica	Heparina sodica	Heparine sodium
Insulin	Insulin	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

Table 7: Other drugs

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History of this recommendation paper

The version presented here was approved at the UIAA MedCom Meeting at Adršpach – Zdoňov / Czech Republic in 2008. It is mainly based on [1]