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Drug storagetemperature fluctuationsin a Dutch Helicopter Emergency Medical Service

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ABSTRACT
Safe use and storage of drugs is essential. Temperature extremes might affect their stability, especially in drugs that require specific storage conditions. Temperature variations have an impact on drugs used in an out-of-hospital setting, with the focus on high temperatures, although its significance is unclear. Our study aims to answer the question whether the drugs used in the Dutch helicopter emergency medical service (HEMS) undergo temperature changes according to the outside temperatures.This was achieved by placing four temperature loggers inside drug bags carried by the HEMS-personnel to record the temperature for one year. Mean kinetic temperatures (MKTs) were calculated per day and compared to outside temperatures. We conducted a review of the literature to analyzethe possible impact of temperature changes on drugs.Subsequently, local practicewas reviewed.The MKTs exceeded the threshold of 25 degrees Celsius (°C)during summer. In winter, the temperatures stayed within storage limitations. Eight drugs were identified to be at risk for degradation when exposed to temperatures above the MKT-threshold. We found no data on temperature-related degradationon 18 of the drugs we carry.
We conclude that the temperatures inside drug storage bags carried by HEMS personnel follow the outside temperature changes in the Dutch temperate maritime climate.The advised storage temperatureswere rarely exceeded. Moreover, this is only of concern for a small portion of our drugs. Local protocols for year-round rotation schemes were revised to warrant drug efficacy on a daily basis.
KEYWORDS:
- Drug storage
- Emergency medical services
- Temperature
- Mean kinetic temperature
- Maritime climate

I. INTRODUCTION

The value of ahelicopter emergency service (HEMS) is invaluable to transport a physician and nurse on-site to deliver expert prehospital care in selected cases of critically ill and trauma patients. Aselection of drugs is needed to provide this care. These drugs are exposed to extremes in temperature in the teams badly airconditioned and isolated helicopter and vehicle.

The prehospital emergency medical care in the Netherlands (population 17 million)is complemented byfour HEMS teams. They have a helicopter and a non-transporting emergency medical service (EMS) vehicle (car) at their disposal.

The Netherlands has a temperate maritime climate (Category Cfb according to the Köppen-Geiger climate classification). Winters can be strong (temperatures dropping below 0 °C), and summers might yield some extremely hot days (up to 35°C). This climate is not only exclusive to north-western Europe, but is also found in selected areas in other countries such as New Zealand, Australia, USA, Argentina, Chilli, South Africa, and Canada(1).

This temperature issue does not only concern our HEMS. Knowledge on the effect of extreme temperatures on drugs used in prehospital emergency medicine receiveslittle attention.(3)Brown et al. showed in a reviewthat thefocus lies on high temperatures. However,the significance of these measurements is not clear.

They encourageevery country with an EMS to at least investigate drug storage policies and to research the effects of outside temperature on drugs.(4)

The objective of this study is toevaluate ifthere is a problem withoutside temperature effectingthe temperature of drugs stored in our HEMS'sequipment bagsyear round. We hypothesizedthat the drug storage temperaturesfollow outside temperature and at times will exceed the maximum and minimumstorage temperatures as advised by pharmaceutical companies.In addition, we performed a literature review on the drugs used by our HEMS.

II. METHODS

The NijmegenHEMS is a civilian servicestationed at the VolkelAir Force Base (AFB)in the Netherlands, covering an area of approximately 10,000 square kilometersand servicing a population of 4.5 million. At the station, drugs are stored in a dedicated storeroom, refrigerated if required. From their storage, four different sets of drugs are made,all being taken to incident locations, are replenishedwhen used or expired.

First, in addition to medical equipment, most drugs are transported in twobackpacks, one in the helicopter and one in the car. Drug contents are listed in table one, including the advised storage temperatures. During transport no drugs are refrigerated. The period that refrigerated drugs are allowed to be stored outside of the refrigerator is strictly observed and respective drugs are replaced as advised by pharmaceutical companies.

Secondly, both the HEMS physician and the flight nurse carry a small drug bag in their uniform. The nurse's bag contains tranexamic acid, phenylephrine, and cefazolin in their ampoules, and the physician's bag contains syringes filled with etomidate, midazolam, fentanyl, and suxamethoniumchloride. The syringes are prepared at the HEMS station by the team members themselves and are discarded and replaced within 24 hours, or earlier when used. These drugs are also listed in Table one.

We recorded the temperatures by placing a Voltcraft DL-101T USB temperature logger (Conrad Electronic SE, Hirschau, Germany)(Figure 1) inside two backpacks and inside the individual drug bags carried by both the HEMS nurse and physician in close proximity of the drug ampoules. The loggers measure 100x23x20mm, and weigh 20g. The loggers have a temperature accuracy of +-1°C within temperature range of 0-40°C, and accuracy of +/-2.5°C when exceeding these ranges.The temperature was recorded automatically every 10 minutes. The recorded data was periodically transferred to a laptop to prevent data loss. Analysis was done using Excel (Microsoft Corp., Redmond, WA, USA).

An observational study was conducted, collecting data during a continuous period fromNovember 14th, 2014 to March 19th, 2016. All four seasons are analysed. Winter, spring, summer and autumn are defined to begin at respectively December 21st, March 21st, June 21st, and September 21st. Data collection of the physicians and nurses drug bag temperature loggers started later on April 15th, 2015. Data from the nurses drug bag temperature logger was lost from November 26th 2015 until end of study due to equipment failure.

From all recorded temperatures a daily minimum, maximum, and mean temperature wascalculated.

The mean kinetic temperature (MKT) is frequently used as a standard measurement for the analysis of temperature effects in pharmacological studies. The MKT is a calculated mean temperature that takes fluctuations into account. This correction is necessary because incidental peak temperatures maynot be an issue, but may contribute to an increased mean temperature. The calculation takes into account the delta activation energy for solids or liquids, the gas constant, and the varying temperatures. A daily MKT was calculated using a prefabricated Excel sheet using the formula shown in Figure two (5, 6)

Outside temperature recordings were retrieved from the online database of the local weather station at VolkelAFB, The Netherlands (7).

A 'Pubmed'search (8)for papers on pharmacological aspects of drugs, drug storage, and effects of temperature on drugs has been conducted.Based on our literature search, we defined drug safety under heat stress as a drug that remains stable when exposed to temperatures above MKT 25°C for more than one month. This MKT of 25°C is in accordance to pharmaceutical advice. Drug safety under cold stress is less well defined in literature, but most often it is stated that once a drug hasbeen frozen, it cannot be used any longer. We defined cold stress as drugs stability when exposed to temperatures below freezing point (0°C) for any period of time.

III. RESULTS

Acomprehensive list of all drugs used by the HEMSincludingstorage temperature recommendations issued by their respective pharmaceutical companies,is shown in table one.Literature results on drug safety under heat and cold stress are included.

The outside temperatures measured by the local weather station at Volkel AFB are plotted against the data from the four temperature loggers in figure three.

During the winter of 2014-2015there were only two loggers running, one in the helicopter bag and one in the vehicle. MKT's remained between the limits of freezing and 25°C. During the spring of 2015 the logger inside the helicopter had one day, and the logger inside the car 4 days with a MKT >25°C.

In the summer of 2015 the temperaturesmeasured by all four loggers were utilized. As shown in figure three, theMKT temperatures followed the course of outside temperatures, thereby exceeding the MKT threshold of 25°C several times (Figure four).For the helicopter, car, physician and nurse the threshold was exceeded on15/92 (16.3%), 30/92 (32.6%), 25/92(27.2%), 17/92 (18.5%) days, respectively. The two temperature loggers inside the EMS vehicle and helicopter reached their most sustained and highest peak between 1-4 July, which corresponded to an acute increase in mean outside temperature from 21.0 °C on the 30th of June to 26.3 °C on the 1st of July, and dropping again to a mean of 21.1°C on the 5th of July. This resulted in four consecutive days of MKTs >25°C.

Only the logger carried by the physician registered one day of MKT >25°C during the fall of 2015. Temperatures in the winter of 2015-2016 again remained within the limits of freezing and 25°C.
The means and range of all data are summarized in table two.

IV. DISCUSSION

One-year serial temperature measurements covering all four seasonsshowthat drug temperatures follow the recorded outside temperatures, hereby exceeding the advised storage temperature to some extent.Some general comments can be made concerning this observational study

Winter was relatively mild (limited amount of days with temperatures below 5°C), thereby limiting exposure of drugs to freezing temperatures. Theupper limitwas never exceededin winter, although the bags occasionally were exposed to the warm air from the helicopter and car heaters.

During summer, the MKT of 25°C wasexceeded on several daysin a row, which implies that drugs may have been at risk of undergoing degradation. (4)Relevance can be argued, sinceall drugs are sterilized at high temperatures for a short period of timeduring pharmaceutical preparation. Unfortunately this study was not designed to evaluate the possible undesirable effectsof drugs exposed to temperature extremes on patients.

During the heatpeaks in July, the temperature inside the vehicle increased more than inside the helicopter, despite the presence of climate control in the car.The climate control, however, is not routinely operational while the car is stationary on the base.Other explanations for this difference are still being sought.

In 2013, de Winter et al. measured temperatures for their ambulance drug storage and found temperatures comparable to our measurements.(2) They used temperature indicator strips to investigate the ampoules inside the ambulance as well as in the storage room, both at room temperature and refrigerated. The Belgian climate is comparable to the Dutch. There are only subtle differences in overall elevation that might contribute to a slight temperature difference.

Degradation of drugs

Pharmaceutical companies guarantee an effective drug content of 90-110% of the amount indicated on the container. Inour HEMS operation, we titrate the drug dosage to clinical effect. Wheneversignificant degradation would have taken place, a larger amount of the solution would be administered to achieve a similar effect and drug dose. Therefore,a limited amount of drug degradation caused by extremes in temperature maynot be clinicallyrelevant.

The amount of degradation was investigated by Gammon et al.(9) They exposed 23 prehospital drugs to either -6°C or +54°C, and they were thermally cycled every 12 hours. Eight drugs were identified that underwent significant drug degradation under the influence of temperature extremes. These were lidocaine, diltiazem, dopamine, nitroglycerin, ipratropium, succinylcholine, haloperidol, and naloxone. Unfortunately,they did not study all other drugs that are carriedby our HEMS.

In addition, De Winter et al.(2) showed that adrenaline and methergine remained stable for at least one year in all situations. Lorazepam became instable at room temperature within four weeks, but remained stable in the ambulance for four weeks. Suxamethoniumchloride remained stable for two months at room temperature but only for one month in the ambulance. Cisatracurium was instable within four months at room temperature, but remained stable for up to four months in the EMS vehicle.

Rocuronium, suxamethoniumchloride, prostin, and oxytocin are advised by their manufacturers to be stored at a temperature between 2°C > T < 8°C and are therefore theoretically more at risk of degradation. For rocuronium it is permitted to store it up to 30°C for a maximum 12 weeks, after which it should be discarded. Once taken out, it should not be refrigerated again. Suxamethoniumchloride may be stored for up to two months at a temperature of up to 30°C. Oxytocin is allowed to be stored for up to three months at a temperature of up to 30°C. Our data shows that it exceeds the limit of 8°C, suggesting that at least these drugs should be rotated at an interval according to the maximum time advised by the pharmaceutical company. Because the MKT exceeds this in all seasons, it means that these drugs need to be refreshed year-round(10).

Drug degradation is mainly of concern for the ampoules carried in the backpacks, not for the prefilled syringes carried by HEMS-personnel, since they are discarded after 24 hours in accordance to current drug protocols.

Toxic degradation products

To date, it is not clear what the clinical effects are of degradation products. Another unmentioned issue is whether potential toxic degradation products exist. We were not able to clarify this.(2, 9, 11)It is assumable that such toxic effectsare not present. Otherwise it is expected that pharmaceutical companies would have given explicit warning in the respective product documentation advising careful handling including strict adherence to theadvised storage temperature range.

Our HEMS has been operational for 15 years and medication ineffectiveness or toxicity due to temperature changes have never reported.

Strengths and limitations

Our study is unique since drug temperature measurements in a Dutch HEMS hasnever been conducted before. Also, all seasons were analysed. This allows for a clear picture of temperature ranges in our specific geographic location, mode of work, and climate conditions.

A limitation of the study is that we did not investigate whether drugs remain stable when stored in HEMS conditions. This approach was chosen, because we initially wanted to explorewhether there even is a problem of exceeding temperature limits. Nevertheless, it remains interesting to know what effects might take place.

Another limitation is that we collected more data on the two vehicle drug bags compared to the loggers carried by HEMS-personnel. However, the summer has the most influence on our drugs, and this season is fully registered. There is also lost data from the flight nurse logger. We have assumedthat themissing-data will not differ much from the physician's logger, since they are always within close proximity of each other and utilize their drug bags in similar fashion.

Our data shows that drugs exceed the MKT-thresholdof 25°C only occasionally. It is unknown what frequency and duration of exceedance would be acceptable within a certain period. However, it is debatable whether it is necessary to invest in our strategies for temperature control. This could involve using isolators,cooling elements, or portable refrigerators, although publications show these measures yield only a minimal effect(4).Moreover,adding this kind of equipment implicates adding weight and requiring additional storage space. This is certainly not desirablefor or less applicable to our helicopter EMS.

Study implications

The potential influence of outside temperature extremes on drugs has been a factor in a recent revision of local protocols for year-round rotation schemes.This increased our confidence in drug efficacy on a daily basis. Some fragile drugs get replaced daily or weekly, regardless of the season.

The data above are encouraging for future investigations on drug degradation in HEMS vehicles in other geographical locations.

V. CONCLUSION

Temperatures inside drug storage bags carried by HEMS vehicles and personnel follow the outside temperature, thereby occasionallyexceeding the advised storage temperatures in the Dutch climate. This is only of concern for a small portionof our drugs. Furthermore, it remains debatable if thiswill result in any clinical implications.However, local protocols for year-round rotation schemes were revised to warrant drug efficacy and match pharmaceutical guidelines.

List of abbreviations:

HEMS: helicopter emergency medical service
MKT: mean kinetic temperature
EMS: emergency medical service
AFB: air force base

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Table 1: Summary of drugs carried by the Nijmegen HEMS, accompanied by advised storage temperatures, and where they remain stable on heat/cold stress according to literature.

Drug(12-15)	Concentration	Storage temperature at HEMS station	Advised Temperature range	Heat stress	Cold stress
Narcotics					
Propofol	10mg/ml, 50 ml	Room	>0 °C T < 25°C	Unknown	Unknown

Midazolam	5mg/ml, 3ml	Room	>0 °C T < 25°C	Yes (16)	Unknown
Etomidate	2mg/ml 10ml	Room	>0 °C T < 25°C	Yes (9)	Unknown
Muscle relaxants					
Rocuronium	10mg/ml 5ml	Cooled	2°C > T < 8°C	Unknown	Unknown
Suxamethonium	50mg/ml 2ml	Cooled	2°C > T < 8°C	No (2, 9)	Unknown
Analgesics					
Fentanyl	0,5 mg / 10 ml	Room	0 °C < T <30°C	Unknown	Unknown
Vasoactive drugs					
Dobutamine	5mg/ml, 50 ml	Room	>0 °C T < 25°C (Not refrigerated)	Yes (3)	Yes (3)
Adenosine	3mg/ml 2ml	Room	No special temperature restrictions	Yes (3, 9)	Yes (3, 9)
Nitroglycerin sublingual	0,4mg/dosis	Room	T < 25°C	No (9)	Yes (9)
Calcium-Gluconate	100mg/ml, 10ml	Room	No special temperature restrictions	Unknown	Unknown
Metoprolol	1mg/ml, 5ml	Room	>0 °C T < 25°C	Yes (3)	Yes (3)
Amiodaron	50mg/ml, 3ml	Room	>0 °C T < 25°C	Unknown	Yes (3)
Atropine	0.5 mg / 1 ml	Room	T < 25°C	Yes (3)	Yes (3)
Magnesium	150mg/ml 5ml	Room	15°C > T < 25°C	Unknown	Unknown
Phenylephrine	0.1mg/ml	Room	No special temperature restrictions	Yes	Yes (17)
Others					
Glucose	50%, 100 ml	Room	>0 °C T < 25°C	Unknown	Unknown
NaCl 0.9%	0.9%	Room	No special temperature restrictions	Unknown	Unknown
Sodium-bicarbonate	8,4%, 100 ml	Room	No special temperature restrictions	Yes (18)	Unknown
Cefazolin	1 gram	Room	T < 25°C	Unknown	Unknown
Ceftriaxone	2 gram	Room	No special temperature restrictions	Unknown	Unknown
Heparine Leo	5000IEml 5ml	Room	>0 °C T < 25°C	No (9)	Unknown
Dinoproston	0.5mg/ml	Cooled	2°C > T < 8°C (refrigerator)	Unknown	Unknown

Tranexamic acid	100mg/ml 5ml	Room	No special temperature restrictions	Yes (19)	Yes
Oxytocin	5IE/ml 1ml	Cooled	2°C > T < 8°C	Yes (20)	Yes (21)
Antidotes/anaphylaxis					
Naloxone	0.4mg/ml 1ml	Room	T < 25°C	No (9)	Unknown
Flumazenil	0.1mg/ml 5ml	Room	T < 25°C -- do not freeze or refrigerate	Unknown	Unknown
Methyl-thioninium (Methylene blue)	10mg/ml 10 ml	Room	Do not freeze or refrigerate	Yes (22)	Unknown
Obidoxime	250mg/ml 1ml	Room	Do not freeze or refrigerate	Unknown	Unknown
Physostigmine	1mg/ml 1ml	Room	15°C > T < 30°C	Unknown	Unknown
Dexamethasone	4mg/ml 1ml	Room	T < 25°C	Yes (18)	Unknown
Clemastine	1mg/ml 2ml	Room	T < 30°C -- do not freeze or refrigerate	Unknown	Unknown
Salbutamol	1mg/ml 5ml	Room	T < 25°C	Yes (23)	Unknown

Table 2: year round measurements in all four bags.

	Winter '14-'15	Spring ‘15	Summer ‘15	Fall ‘15	Winter '15-'16
Min (all loggers)	5.00	6.10	6.90	5.70	5.40
Max (all loggers)	22.40	39.70	47.20	36.40	37.30
Min MKT (all loggers)	5.48	8.53	14.45	6.41	6.63
Max MKT (all loggers)	18.32	26.93	33.57	25.84	24.82
Mean MKT (all loggers) (SD)	11.88 (2.18)	18.80 (4.04)	22.62(3.30)	17.06(4.23)	14.87 (4.58)
Min outside	-5.60	-2.90	5.80	-3.20	-9.50
Max outside	17.80	33.60	36.90	18.50	14.90
Mean outside(SD)	4.13 (2.96)	11.54 (3.89)	17.67 (3.59)	9,79 (3.27)	4.85 (3.58)

All measurements are in degrees Celsius (°C)
MKT = mean kinetic temperature
Min = minimum
Max = maximum

Figure 1: Voltcraft DL-101T USB temperature logger

Figure 2: mathematical calculation of MKT, figure reproduced with permission of Vacker LLC(6)

$$TK\,[K] = \frac{-\Delta H\,/R}{\ln\left(\dfrac{\sum_{1}^{n} \exp\left(\dfrac{-\Delta H}{R \cdot T_n}\right)}{n}\right)}$$

ΔH is the activation energy
R is the universal gas constant
= 83.14472 KJ/Mol
T is the temperature in degrees K
n is the total number of (equal) time
period over which data are collected

Figure 3: overview of MKT values compared to MKT threshold and the mean outside temperature

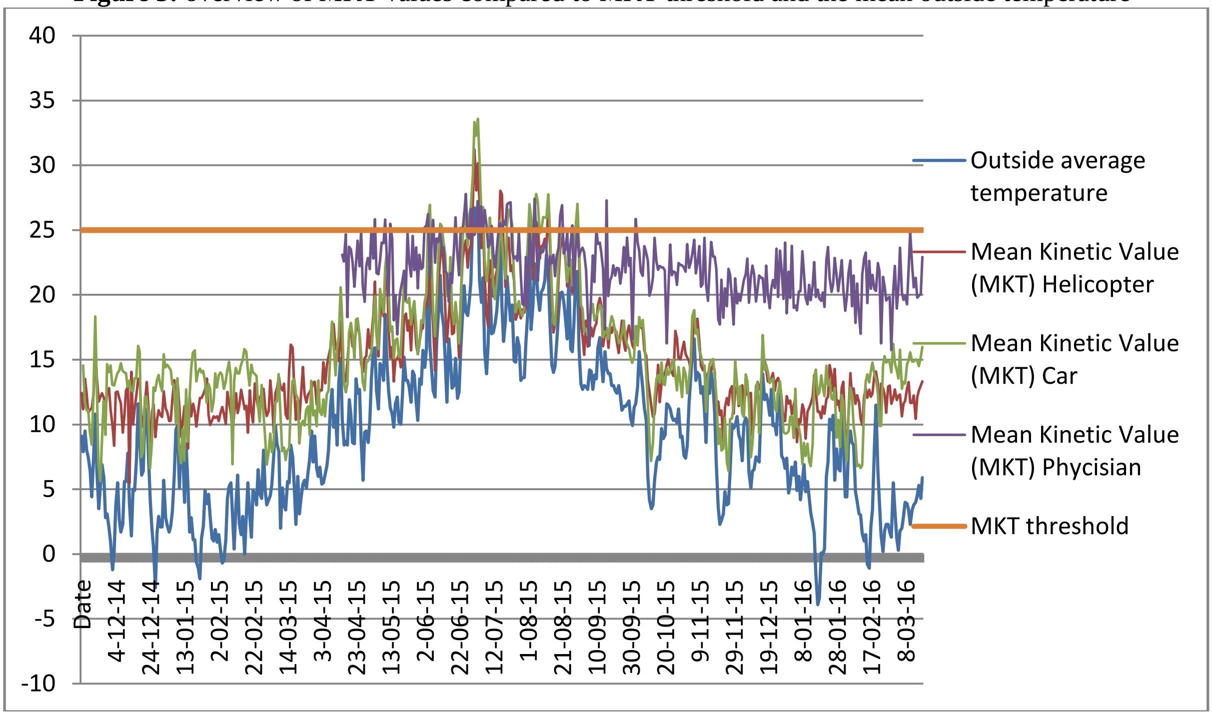
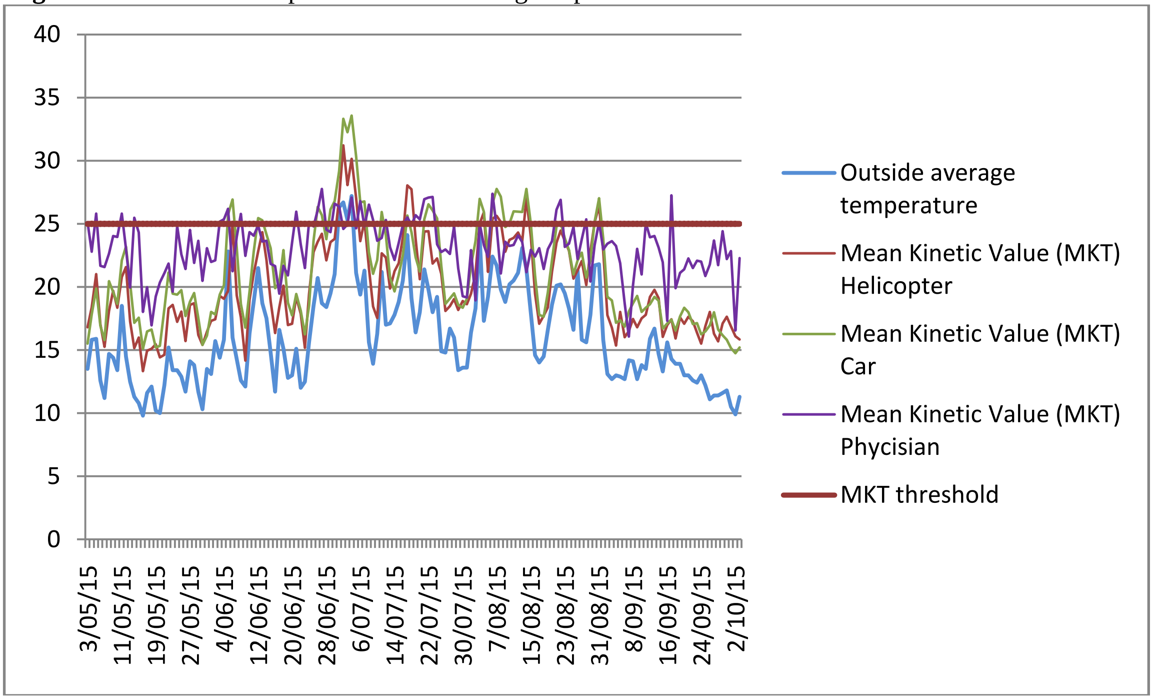


Figure 4: zoom-in on temperature curves during the period where MKT threshold of 25 °C was exceeded.



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