Visiting bags: a labile thermal environment

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Abstract

Objective—To define usual colour and site of storage of visiting bags in general practitioners' cars and to investigate effect of these variables on temperature inside bag.

Design—Questionnaire to general practitioners; serial temperature measurements from paired black visiting bags at different storage sites and from bags of different colour.

Setting—South Devon coastal town during May and June.

Subjects—200 general practitioners, of whom 145 returned legible questionnaires.

Main outcome measures—Bag colour, duration and site of storage, temperature inside black bags at defined storage sites, and effects of bag colour on internal temperature.

Results—111 (77%) of the general practitioners carried a black visiting bag, and 76 kept their bag in their car all day. The bag was coolest in the car boot, but irrespective of storage site, maximum internal temperature of the bag was always over 25°C and reached up to 80°C. Spraying a black bag silver significantly reduced the bag's internal temperature (mean difference 8.37°C (95% confidence interval 6.68 to 9.86°C) df=59, $t=10.29$, $P<0.001$).

Conclusions—General practitioners should use a silver coloured visiting bag; when visiting, they should store it in their car boot; at other times they should remove it to a cooler site.

Introduction

Home visiting remains an important component of general practitioners' work,^{1,2} and they must be adequately equipped with pharmacologically viable formulations to give immediate treatment if required. There is consensus on which drugs should be carried by visiting general practitioners,^{3,5} but little work has been done on the temperature to which these drugs are exposed and its effect on their stability.⁶ Stability testing of drugs sent to Africa and Thailand stored at temperatures of up to 45°C showed a reduction in potency of both adrenaline and ergometrine maleate.⁷⁻⁹ During distribution in Sudan the potency of ergometrine fell by 47% and the activity of adrenaline was almost undetectable.⁷

In a pilot study we recorded a range of temperatures between -4°C and 33°C in a black visiting bag inside a car over 24 hours in February. The commonly accepted temperature range quoted by manufacturers for most formulations carried by general practitioners is 0-25°C.¹⁰ We were concerned that substantial thermal damage would result from storage of drugs in cars, particularly during the summer. We therefore conducted this study to define the usual colour of doctors' visiting bags and the usual duration and site of storage of the bags in a car; to measure the temperature inside a typical visiting bag in a car; and to investigate the

effect of storage site in a car and bag colour on the bag's internal temperature.

Subjects and methods

QUESTIONNAIRE

We sent a simple, one page questionnaire to 200 general practitioners in the area of south Devon between Exeter and Torbay. Table I shows the questions asked.

TEMPERATURE MEASUREMENTS

We measured temperatures in two identical black visiting bags—made from acrylonitrile butadiene styrene and measuring 42 cm×32 cm×13 cm (Custom Cases, Hertfordshire)—inside a white hatchback car (Ford Escort) that was parked outside our surgery in an unshaded site. The maximum temperature and hours of sunlight for the recording days were provided by the Teignmouth meteorological station, five miles from our surgery. Figure 1 shows the storage sites where we measured temperatures, comparing paired sites with the two identical visiting bags. To investigate the influence of bag colour on its internal temperature we sprayed one of the two bags with silver aerosol spray paint. We then placed the cases side by side on the back shelf of the car (the hottest storage site). We compared paired data for each recording period with paired t tests.

We measured temperatures with a SQ2-4U Squirrel meter/logger (Grant Instruments, Cambridge) and factory calibrated thermistors (temperature range

TABLE I—Summary of replies by 145 general practitioners* to questionnaire about use of visiting bag. Values are numbers (percentages) unless stated otherwise

Questions and responses	
Colour of bag (n=145*):	
Black	111 (77)
Silver	5 (3)
Other	29 (20)
Manufacturer of bag (n=68*):	
Custom Cases	28 (41)
Other	40 (59)
Storage site of bag in car (n=145*):	
Floor	72 (50)
Boot	43 (30)
Rear seat	9 (6)
Front seat	21 (14)
Longest time bag stays in car during working day (n=141):	
Median (range)	8 h (5 min-24 h)
Awareness of thermal degradation of drugs carried (n=145*):	
Yes	31 (21)
No	114 (79)
Thermal change noticed in drugs (n=38):	
Molten suppositories	23 (61)
Discoloration of prochlorperazine	10 (26)
Other	5 (13)
Emergency drugs stored in bag (n=144*):	
Yes	119 (83)
No†	25 (17)
Regular audit of drugs carried for expiry dates (n=145*):	
Yes	114 (79)
No	31 (21)

*Not all questions were answered by all respondents.

†Most of these stored their emergency drugs in separate box in car boot.

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-15°C to 85°C, accuracy within 0.4°C). Thermistors were taped to vials containing 2 ml water—to simulate injectable formulations—that were placed in slots cut in foam fitted into the top of each bag, simulating the normal storage of drugs. A 5 mm air gap between the bag's top surface and the vial prevented direct conduction of heat. Ambient temperature was recorded from a shaded location beside each bag. Internal and ambient temperatures were measured simultaneously from both bags at 10 minute intervals over about nine hours of daylight on any one day, a period similar to that which most general practitioners kept their bag in their car.

Results

QUESTIONNAIRE

Of the 200 questionnaires sent out, 150 were returned and five were discarded because of confusing and illegible replies. Not every section was consistently answered. Table I summarises the replies.

TEMPERATURE MEASUREMENTS

Table II shows that the internal temperature of the bag was always higher than the local ambient temperature regardless of the site of storage (mean

FIG 1—Diagrammatic representation of storage sites for visiting bag in car

FIG 2—One day's recording of temperatures of black visiting bags stored in boot or on back shelf of car

Practice implications

- Most general practitioners use a visiting bag to carry drugs for house calls, and this may be subjected to extremes of temperature while left in a car
- In this study, most of the general practitioners surveyed used a black visiting bag and kept it in their car all day
- The internal temperature of a black visiting bag stored in a car was always higher than ambient temperature and frequently exceeded drugs' thermal stability ranges
- Spraying the case silver significantly reduced its internal temperature
- General practitioners should put their visiting bag in the boot or on the floor of the car when visiting, remove the bag from the car at other times, and use a silver coloured bag

difference 8.42°C (95% confidence interval 7.54°C to 9.31°C), $df=298$, $t=18.66$, $P<0.001$). This difference was greatest on the back shelf, where the highest internal temperature (80°C) was recorded. Even when the bag was stored in the boot its internal temperature reached nearly 40°C on several occasions. Irrespective of storage site the bag's maximum internal temperature was always more than 25°C. Figure 2 shows an example of one day's recordings. Storing the bag in the car boot kept its internal temperature significantly lower than did storage at any other site except for the back floor.

Spraying the visiting bag silver significantly reduced its internal temperature (mean difference between bags 8.37°C (6.68°C to 9.86°C), $df=59$, $t=10.29$, $P<0.001$; maximum difference 16°C (59°C v 75°C)).

Discussion

Most of the general practitioners used a black visiting bag that contained emergency drugs and was kept in their car for considerable periods. Such drugs are hotter than the ambient temperature in the car and reach temperatures that exceed their stated thermal stability range.^{3 10 11} This may have medicolegal implications, but, more importantly, the thermal stress may affect the efficacy of formulations such as adrenaline which are used infrequently but with the expectation of lifesaving effectiveness. The stability testing of a formulation before a product licence is granted does not seem to match conditions that the drug will commonly be exposed to. The tripartite guidelines of the International Conference of Harmonisation recommended accelerated testing of drugs at 40°C for six months and long term testing at 25°C for 12 months,¹² temperatures that were exceeded in this study.

We took care to prevent the conduction of heat from

TABLE II—Maximum temperatures recorded in visiting bags at different storage sites in car. Simultaneous recordings made at two sites for comparison

No of recordings	Maximum temperatures at paired storage sites						Difference between internal temperatures (°C)		Meterological conditions	
	Cooler site			Hotter site						
	Site	Ambient (°C)*	Internal (°C)†	Site	Ambient (°C)*	Internal (°C)	Mean (95% confidence interval)	P value	Maximum temperature (°C)	Hours of sunlight
38	Boot	33.8	39.4	Back shelf	60.2	80.2	28.9 (19.42 to 38.38)	<0.001	24.1	14.1
59	Boot	27.4	35.4	Back seat	37.0	59.0	14.0 (10.36 to 17.64)	<0.001	17.6	12.8
48	Boot	31.8	37.8	Back floor	27.4	42.2	0.2 (0.14 to 0.26)	0.5	20.5	14.4
45	Boot	34.6	38.2	Front seat	47.8	65.0	12.5 (8.74 to 16.26)	<0.001	22.2	14.7
51	Boot	26.2	29.4	Front floor	25.4	29.8	1.1 (0.8 to 1.4)	<0.001	19.7	4.2
57	Back seat	39.4	49.8	Front seat	41.0	53.0	0.7 (0.52 to 0.88)	0.3	21.9	9.8
47	Back floor	28.6	39.4	Front floor	29.0	52.2	2.6 (1.83 to 3.37)	<0.001	21.3	12.6

*Recorded beside bag. †Recorded inside bag.

the skin of the visiting bags to the vials, but this might occur if doctors were to cut deep slots into the foam filled lids of their bags. Thus, our findings may underestimate the temperatures to which vials are exposed.

* Absolute temperature is not the only factor that can influence a formulation: the rate of temperature change, cyclical temperature change, and vibration will modify some preparations. Cooling a suspension can promote particle growth, and seed crystals then act as a focus for further crystallisation during each freeze-thaw cycle. Emulsions are vulnerable to creaming or flocculation at extremes of temperature, while vibration may cause coalescence; all of which can modify biological activity.

To minimise the risk of thermal damage to the contents of their visiting bag general practitioners must be confident that sample drugs have not previously been thermally damaged in a sales representative's sample case; they should keep their bag in the boot or on the floor of their car when visiting and remove it from the car at other times; and they should use a silver coloured bag, which is significantly cooler than an otherwise identical black bag.

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THE NOBEL PRIZES

Yellow fever triumph and tragedy

"Buy a case of Scotch and watch the Dodgers," was Max Theiler's response in 1951 when a reporter asked what he was planning to do with the money from his newly announced Nobel prize.

A modest and likeable man, Theiler was honoured for developing a potent vaccine against yellow fever. But while "yellow-jack" brought fame and fortune to one scientist, it meant tragic failure for contemporary researcher Hideyo Noguchi. Following a false trail in pursuit of the micro-organism responsible for the infection, Noguchi succumbed to yellow fever himself—committing a microbiologist's *hara-kiri*, some have suggested, once he realised his failure.

Max Theiler was born in 1899 on a farm near Pretoria. In 1919, after premedical studies at Capetown University, he arrived in London and began a medical course at St Thomas's Hospital. Not working terribly hard, but helped by £20 (\$30) a month from his father, he spent as much time as possible in art galleries, going to the theatre, and reading Ibsen, Chesterton, Shaw, and Wells.

Theiler was fired with enthusiasm for microbiology while taking a postgraduate diploma at the London School of Hygiene and Tropical Medicine. The spark came from *Infection and Resistance*, a textbook by the United States bacteriologist Hans Zinsser, author of the classic *Rats, Lice and History*. Shortly afterwards, Theiler was offered a post at Harvard University, which he took up in 1922. Once there, he struck up a friendship with Zinsser and (in the midst of prohibition) the two were soon exchanging recipes for home brewing.

Theiler also found himself embroiled in a spirited debate about the cause of yellow fever. Noguchi, born in Japan but then working in New York's Rockefeller Institute, insisted that the culprit was a spirochaete. Theiler favoured a virus, which he managed to grow in mice. When his paper describing these studies appeared in *Science* in 1930, other researchers questioned his conclusions. But then he made two key discoveries—that serum from recovered patients neutralised his virus, which also became attenuated over time when grown in mice.

While others remained sceptical, Wilbur Sawyer of the Rockefeller Foundation in New York was deeply impressed and tempted Theiler away to a new post at double his previous salary. The foundation then launched a worldwide survey of the distribution of yellow fever, using Theiler's neutralisation test

to identify infected individuals.

Exploiting his discovery of attenuation, Theiler began work towards a vaccine, growing the virus in tissue culture. Three years and thousands of cultures later, a flask labelled 17D yielded the virus that was to form what the *BMJ* (1981;282:1735) has called "the best and safest of all viral vaccines in use today." In 1936 Theiler tried it on himself and measured his rise in antibody titre. Four years later, field tests were complete and over the next seven years the Rockefeller Foundation produced over 28 million doses. Combined with measures to contain mosquitoes, Theiler's vaccine has kept in check an infection which, at the turn of the century, was still rampant in large areas of Africa, South America, and the Caribbean.

When Hideyo Noguchi first became interested in yellow fever he had already achieved several major breakthroughs, including the first cultivation of the spirochaete of syphilis and key advances in understanding trachoma and scrub typhus. But yellow fever was to be his downfall. He isolated a spirochaete that he believed to cause the disease and named it accordingly. Injected into guinea pigs, it certainly produced something like yellow fever. Theiler, however, soon proved that this was the agent of a quite different condition, the type of jaundice known as Weil's disease.

But Noguchi stuck to his guns. He did so even when the Rockefeller Foundation team failed to find his spirochaete in patients infected with yellow fever in the tropics, and when Adrian Stokes, working in the Gold Coast, transmitted yellow fever to monkeys using material passed through a filter sufficiently fine to exclude spirochaetes and other bacteria but not viruses. Soon afterwards, in September 1927, Stokes contracted the infection and died. The following year, Noguchi left New York for Accra, saying "I will win down there or die." For months he peered at yellow fever blood samples for evidence of his spirochaete, but without success. Then the real organism, yellow fever virus, claimed his life too.

Max Theiler was honoured with the 1951 Nobel prize for physiology or medicine. Noguchi was also considered for the award when his earlier studies suggested a bacterial origin for yellow fever. As we now know, however, he came close to being honoured for a mistaken piece of work. His last recorded words, on his death bed, were: "I don't understand."—BERNARD DIXON is a freelance science writer