

Adrenaline degradation in general practice

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SUMMARY

The general practitioner's (GP's) doctor's bag is exposed to extreme temperatures that may affect the stability of the drugs it contains. Adrenaline (1:1000 solution) is more stable than previous studies would suggest. GPs carry out-of-date drugs despite stating that they regularly check expiry dates.

Keywords: drugs; drug expiry date; drug storage; medical materials and equipment; doctor's bag.

Introduction

ADRENALINE is a key drug in the treatment of cardiac arrest, anaphylaxis and life-threatening asthma. These are all conditions a GP may meet when carrying out home visits, and the literature highlights the need to be prepared for such eventualities.¹ There is evidence to demonstrate that the temperature inside a black doctor's bag can reach 80°C.² Thermal stress can degrade adrenaline in the setting of pre-hospital care.³⁻⁵ Stability testing of drugs sent to the Sudan⁶ showed almost no adrenaline activity after storage in temperatures up to 45°C and studies on adrenaline in preparations of local anaesthetic have demonstrated substantial reduction in adrenaline activity at temperatures of 37–50°C.⁷⁻⁹ This investigation aimed to answer whether adrenaline carried in the doctor's bags of GPs in the Perth (Western Australia) metropolitan area, where summer temperatures reach nearly 40°C, is thermally degraded.

Method

General practitioners were randomly selected using the Perth metropolitan telephone directory until a hundred GPs who carried out home visits were recruited. The GPs were requested to exchange the next-to-be-used vial of adrenaline from their doctor's bag with a fresh sample and answer a simple questionnaire. Table 1 shows the questions asked. The adrenaline and questionnaires were returned in a stamped addressed envelope. Non-responders were followed up by one telephone call after two weeks. Returned vials were then stored at 4°C before batch analysis using reverse phase high-performance liquid chromatography and electrochemical detection.¹⁰

The temperature inside a black doctor's bag placed in the rear of a white station wagon during a two-week period in October was recorded using a Datataker-5 single-channel logger and

attached factory-calibrated thermistor, range 0–100°C ($\pm 0.4^\circ\text{C}$), at 10-minute intervals throughout this period (Data Electronics, Australia, Ltd). The daily weather conditions for the period of temperature measurement were provided by Perth Meteorology bureau, 15 km from our sampling area. Ethical committee approval was granted and the research was supported by Astra Pharmaceuticals Ltd. Data were analysed using Epi Info version 5.01.

Results

Seventy-seven questionnaires were returned, 65 of which were complete and accompanied by a GP's vial of adrenaline. The results are summarized in Table 1. Ninety-five per cent of GPs in this sample carried a doctor's bag containing emergency drugs; 65% of these carried a black doctor's bag and 57% usually kept their bag in the car when carrying out visits. A large minority kept their bag in the car all the time (38%).

The vials returned by GPs had been in their bags for an average of 6.7 months – including the summer months, when shade temperatures reach close to 40°C. A maximum temperature of 65.4°C was recorded inside a black doctor's bag stored in the rear of a vehicle in direct sunlight, on a day enjoying a maximum temperature of 29°C. The mean activity of adrenaline vials was 92.9%, range 100.6–62.6%; 12 (18.5%) of the returned vials had an activity of less than 90%. No colour change was seen in any of the vials.

There was a strong inverse correlation between adrenaline activity and the number of months by which the adrenaline vial returned by a GP was out of date (Spearman's correlation coefficient = 0.493, $P = 0.014$). The most degraded vial, with an activity of 62.6%, had an expiry date more than five years prior to the study. There was no correlation between bag colour and degradation. One-third (20) of the vials had expiry dates prior to the month during which the study was carried out despite 92% of the GPs stating that they checked the expiry dates of the drugs in their doctor's bags.

Discussion

Temperatures in excess of 60°C have been recorded in GPs' doctor's bags in Australia.¹¹ We feel confident that the maximum in-bag temperature recorded in this study (65.4°C) could be exceeded during hotter summer days; it is much higher than the recommended maximum storage temperature for adrenaline of 25°C.¹²

There was at least a 10% reduction of adrenaline activity in 18.5% of the returned adrenaline vials; the greatest reduction (to 62.6% of activity) was in a vial nearly five years past its expiry date. As expected, the more out of date the adrenaline the greater the degree of degradation. The usual degradation pathway for adrenaline is via oxidation to adrenochrome, a pink-brown oxidative product, toxic to myocardium in high concentrations.¹³ We observed no colour change, suggesting that adrenochrome was not present in noticeable concentrations. These data may have pharmaceutical significance, but for GPs who use adrenaline in an emergency, at a dose sufficient to produce a desired response, even a 40% loss in effectiveness is probably not clinically important.

Cycled thermal stress of 70°C over a 12-week period caused a significant degradation of 1:10 000 adrenaline with an associated loss in biological activity;³ there was no evidence of a significant

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Table 1. Summary of replies from 65 GPs regarding the use of their doctor's bag and the activity of the adrenaline kept in the bag. Values are numbers (percentages).

Questions and responses	n (%)
Bag colour:	
Black	42 (65)
Brown	9 (14)
Other	14 (21)
Time bag spends in the car:	
All the time	25 (38)
Daytime only	3 (5)
Only between visits	37 (57)
Awareness of thermal degradation of drugs carried:	
Yes	9 (14)
No	56 (86)
Emergency drugs stored in the bag:	
Yes	62 (95)
No	3 (5)
Expiry dates checked:	
Yes	60 (92)
No	5 (8)
Visits per month:	
Median (months)	13 (2-200) ^a
How long had the adrenaline been in the bag:	
Median (months)	4 (1-48) ^a
Activity of adrenaline:	
Mean	92.97 (SD = 6.25)

^aRange rather than percentage.

change in 1:1000 adrenaline, which had a higher concentration of the antioxidant (sodium metabisulphite) and was not pH-buffered. All the adrenaline 1 ml 1:1000 ampoules returned in our study were manufactured by Astra Pharmaceuticals and contained adrenaline acid tartrate, with sodium metabisulphite as an antioxidant, in solution with sodium chloride and water. The concentration of antioxidant affects thermal stability, and the lack of adequate antioxidant in adrenaline solutions used in dental practice may account for the thermal instability demonstrated in this setting.⁶⁻⁸

In a clinical practice where vials of adrenaline are carried in GPs' bags that are stored in vehicles for considerable periods of time, often beyond their expiry date, and exposed to temperatures far in excess of their stated thermal stability range, 1:1000 adrenaline is more stable than previous reports suggest. Nonetheless, this study demonstrates the need for GPs to check and replace expired drugs as other formulations may be more susceptible to thermal stress.

References

1. Avery A, Pringle M. Emergency care in general practice. *BMJ* 1995; **310**: 6.
2. Rudland SV, Jacobs AJ. Visiting bags: a labile thermal environment. *BMJ* 1994; **308**: 954-956.
3. Grant TA, Carroll RG, Church WH, *et al.* Environmental temperature variations cause degradation in epinephrine concentration and biological activity. *Am J Emerg Med* 1994; **12**: 319-322.
4. Palmer RG, Zimmerman J, Brown PC, Clawson JJ. Altered states. The influence of temperature on prehospital drugs. *J Emerg Med Ser Journal of Emergency Medical Services* 1985; **10**: 29-31.
5. Church WH, Hu SS, Henry AJ. Thermal degradation of injectable epinephrine. *Am J Emerg Med* 1994; **12**: 306-309.
6. Abu-Reid IO, El-Samani SA, Hag Omer AI, *et al.* Stability of drugs in the tropics. A study in Sudan. *International Pharmacy Journal* 1990; **4**: 6-10.

7. Kelly JR, Dalm GW. Stability of epinephrine in dental anaesthetic solutions: implications for autoclave sterilisation and elevated temperature storage. *Mil Med* 1982; **150**: 112-114.
8. Fry BW, Ciarlone AE. Concentrations of vasoconstrictors in local anaesthetics change during storage in cartridge heaters. *J Dent Res* 1980; **59**: 1163.
9. Fry BW, Ciarlone AE. Storage at body temperature alters concentration of vasoconstrictors in local anaesthetics. *J Dent Res* 1980; **59**: 1069.
10. Goldstein DS. Modified sample preparation for high performance liquid chromatographic-electrochemical assay of urinary catecholamines. *J Chromatogr B Biomed Appl* 1983; **275**: 174-177.
11. Watson DS, Sunderland B. Summer temperature in a doctor bag and emergency drug stability. *Med J Aust* 1978; **2**: 297-298.
12. *ABPI Data sheet compendium 1993-94*. London: Datapharm Publications, 1993.
13. Rump AF, Klaus W. Functional effects of adrenochrome in isolated rabbit heart. *Pharmacol Toxicol* 1995; **77**: 102-105.

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