National Ambulance Resilience Unit
NARU

NHS

Nitrite Poisoning and Methylene Blue

NARU Position

31st of July 2024

Regulation 28: Report to Prevent Future Deaths

The National Ambulance Resilience Unit (NARU) received a Regulation 28; Report to Prevent Future Death from Crispin Giles BUTLER; senior Coroner for the coroner area of Buckinghamshire dated 7th June 2024.

This related to the tragic death of Fern Elizabeth FOSTER on 8th July 2020. Her cause of death is noted as [redacted] poisoning and a narrative conclusion was reached.

NARU has been named and requested to respond by 2nd August 2024. This is alongside other relevant organisations. These are namely:

- National Ambulance Service Medical Directors (NASMeD),
- Association of Ambulance Chief Executives (AACE),
- NHS England (NHS Pathways),
- National Coding Group (Central Ambulance Team),
- Emergency Call Prioritisation Group (ECPAG)

NARU is not a legal entity. NARU is an organisation created through a contractual agreement between NHS England and London Ambulance Service (LAS). Prior to April 2024 this contractual agreement was held with West Midlands Ambulance Service University NHS Foundation Trust (WMASUFT).

Under that contract, NARU is required to escalate all Regulation 28: Prevention of Future Death requests it receives to NHS England for processing and management.

The Regulation 28; Prevention of Future Death report was received by NARU on 7th June 2024.

The next step, corporately is for NARU, is to contact the office within our host Trust that deals with Regulation 28: Prevention of Future Death requests so they can provide the appropriate response on behalf of the organisation and Trust. This position statement forms part of that submission to our host Trust.

The specific section of the Regulation 28: Prevention of Future Death report was to address the second point of the Matters of Concern.

This was

'*The carrying by ambulance services of appropriate antidote medication for on-scene administration (such as Methylene Blue), whilst trialled elsewhere, is not part of regional or national protocol. Swift access to this in circumstances where* [redacted] *ingestion is suspected, and timings mitigate against survival by the time of arrival at the nearest Emergency Department, could prevent future deaths in some cases.*'

Firstly, it must be noted that NARU has no authority to mandate the carriage of any specific drugs, including antidotes, by NHS Ambulance Services. Except for those decided by NHS Resilience (EPRR) as part of the Mass Casualty Vehicles (MCV) which are part of the national interoperable capabilities for emergency preparedness to major incidents.

The decision as to which drugs each ambulance service carries is taken by that individual NHS ambulance Trust with authorisation from the Executive Medical Director in conjunction with Chief Pharmacist.

The ambulance service medical directors meet regularly within NASMeD to share learning and practice development. The NARU Medical Advisor; [redacted], is a non-voting member of NASMeD and regularly attends these meetings.

The clinical practice of ambulance service paramedics is supported by the Joint Royal Colleges Ambulance Liaison Committee (JRCALC) which is hosted by AACE. JRCALC publish Clinical Practice Guidelines for UK ambulance services. Historically, these guidelines were published in hard copy with supplements. Currently they are provided in an App form (JRCALC Plus App) to facilitate regular updates.

Each ambulance Trust can adopt these clinical practice guidelines in totality or modify sections in line with their own local practice and clinical governance procedures. This is under the discretion of the Executive Medical Director and senior clinicians.

Whilst not having a statutory role, NARU is keen to facilitate clinical development to benefit patient outcomes, particularly in the realm of response to complex and major incidents. NARU do provide oversight for the Hazardous Area Response Teams (HART) within each English ambulance service. These are teams of paramedics with additional training and safe systems of work to allow access to deliver patient care in environments that standard paramedics may be unable to access due to risk to themselves. This would include incidents with hazardous materials and chemical exposure. Whilst NARU can direct the safe system of work, it has no ability to direct clinical practice. The only expectation is that the HART paramedics can deliver the standard skill set within JRCLAC clinical practice. However, a number of ambulance Trusts have expanded the skill set of their HART paramedics under the discretion of the medical director as they perceive a need for an increased level of clinical care to the patients HART may attend.

The clinical leadership of ambulance service HART therefore represent a useful resource to gain insight into advances in clinical practice for HART paramedics and NARU holds intermittent Clinical Subgroup meetings to act as a conduit for information sharing on clinical practice.
The information gained from these meetings can then be fed into NHS Resilience, NASMeD and JRCALC. This facilitates cross organisational learning and can be used to improve clinical practice within all ambulance services.

The next NARU Clinical Subgroup meeting is scheduled for September 2024, though the exact date is yet to be confirmed.

The proposed agenda will include the management of toxicological incidents and subject matter experts in the field will be invited to contribute to the discussions. The management of [redacted] poisoning will be discussed together with the potential role of methylene blue within HART practice.

Part of this discussion will include a review of the Regulation 28; Prevention of Future Death reports relating to [redacted] poisonings, together with a presentation from WMASUFT around their experience following the introduction of methylene blue into HART practice.

WMASUFT introduced methylene blue for the treatment of [redacted] poisoning by HART in July 2020. This was following a Serious Incident review and Regulation 28; Prevention of Future Death report sent to the Trust form a case of nitrite poisoning in 2019.

Experience from this project was received by the NARU Medical Advisor on 16th July 2024. In summary, since July 2020 WMASUFT HART have attended 9 cases of suspected [redacted] poisoning. This should be considered in the context of total call volume, representing ~1 in 0.5 million 999 calls. Of those 9 cases:

- 4 received methylene blue:
  - 3 received methylene blue at scene and survived to the Emergency Department
  - 1 received methylene blue in the Emergency Department having been conveyed in cardiac arrest. They did not respond to treatment and were declared deceased.
- 5 did not receive methylene blue:
  - 4 were deceased on arrival of the ambulance responders.
  - 1 did not have signs or symptoms of significant nitrite toxicity and had low recording of methaemoglobinaemia.

The NARU Clinical subgroup will collate the evidence and present a report to NASMeD for consideration. This will be delivered in conjunction with guidance from subject matter experts, principally toxicologists from the National Poisons Information Service (NPIS) that can be reviewed by NASMeD and AACE representing JRCALC.

In addition, it should be noted that AACE have approached the NPIS for national expert opinion regarding the carriage of methylene blue on ambulances. According to the response received by the NARU Medical Advisor on 24th July 2024, this was discussed at the NPIS Clinical Standards Group on 4th July 2024. The key part of the response is as follows:

'*There is currently no evidence to recommend the routine carrying of this antidote by ambulances. The evidence from the pilot study was insufficient to change NPIS policy but we are interested in the possibility of specialist ambulances carrying it. More studies and evidence are required.*

In most cases, the most useful approach will be for paramedics to immediately administer 100% O2 through a NRB mask and then rapidly transfer the patient to an emergency department ready to assess and manage the patient.'

In view of this opinion the NARU Clinical Subgroup will discuss the potential for wider expansion of the WMASUFT trial in a unified format across a number of ambulance Trust HART to gain the additional data that would provide evidence to support changes in practice recommendations. This would be subject to agreement from the respective ambulance service Medical Directors to support their HART units participating.

This response to the Regulation 28 has been drafted in line with a more detailed clinical response written by the NARU Medical Advisor, [redacted], a Consultant in Emergency Medicine and Pre-Hospital Emergency Medicine. This report is attached as Appendix 1 to this response. [redacted] is willing to be contacted should you require any additional information relating to his report or this response.

We wish to express our sincere condolences to the family and friends of Fern for their loss.

Appendix 1

This has been compiled by our Medical Advisor, [redacted] MBE BSc(Hons) MBChB FRCS FRCEM DipIMC DipHEPRR

The reference sources for this are from the National Poisons Information Service (NPIS) via the Toxbase website and additional open-source literature from the UK and worldwide.

Current NARU Position Regarding Methylene Blue

Methylene blue (methylthioninium chloride) is a recognised treatment for Methaemoglobinaemia (MetHb). This is when the iron contained in the haemoglobin molecules changes from Fe2+ to Fe3+. This results in a reduced capacity of the haemoglobin in the red blood cells to carry oxygen from the lungs to the body. This is because of two main effects that result from the change in haemoglobin. Firstly, the MetHb cannot carry oxygen as efficiently as normal Hb. Secondly, the MetHb does not release oxygen easily to the tissues. Therefore, this results in the tissues being unable to receive oxygen.

There is a normal low level of MetHb within normal healthy people, usually less than 1%. This occurs as a result normal effects on the body. As a result, the body has systems that can convert MetHb back to normal Hb via enzymes, though these systems can only cope with a small amount of MetHb and will be overwhelmed by significant amounts.

Therefore, the greater percentage of haemoglobin that is methaemoglobin (MetHb) the more severe the symptoms and threat to life. The effect of MetHb causing lack of oxygen can be worsened if there are other illnesses that reduce the ability of the body to absorb and distribute oxygen. These would include anaemia (low haemoglobin), heart disease and lung disease.

The harmful clinical effects are related to the percentage of MetHb within the bloodstream. The higher the percentage, the more serious the effects.
The exact percentage that clinical signs and symptoms develop does have a degree of variation between patients and a summary of the published guidance below highlights the different

Percentage MetHb	Patient Appearance	Clinical Symptoms
<10%	Normal	No symptoms
10-20%	Slight Cyanosis (blue tinge to skin)	Mild symptoms, slight shortness of breath, mild headache
20-30%	Cyanosis and chocolate brown blood when sampled	Anxiety, headache, lightheaded, slight increased pulse rate
30-50%	Profound cyanosis	Confusion, fast pulse and breathing rate, low blood pressure
50-70%		Unresponsive (coma) or seizures, abnormal heart rhythms, slowing of breathing
70%		Death

The clinical appearance of the patient; blue grey skin discolouration is useful but does not equate accurately to MetHb levels. The recognition of cyanosis, blue tinged skin, in patients with pigmented skin can be challenging.
However, the combination of cyanosis and ‘chocolate brown blood, seen when a patient has an intravenous cannula inserted can be used to suggest the level of MetHb is over 15-20%.

In addition to the lack of oxygen (hypoxia) high levels of MetHb cause acidosis and breakdown of the red blood cells leading to further harm.

Diagnosis of Methaemoglobinaemia

Recognition of MetHb levels is best assessed by a blood test to accurately measure the MetHb level. This is easily done in hospital on blood gas analysers. This equipment is expensive in initial cost and maintenance. Therefore, these are not commonly carried in the prehospital environment. However, a few air ambulance critical care teams carry small mobile versions of this equipment, though again they are costly to buy and maintain.

Waveform oxygen saturation monitors are carried on all front-line vehicles. These use red-infrared spectroscopy to give an estimate of how much oxygenated and deoxygenated Hb is in the blood stream of the patient. In normal health the level of oxygenated would be over 95%. Though in those with chronic lung disease and some other conditions a level of 88%-92% might be acceptable and tolerated by the patient. These normal oxygen saturation probes are not designed to monitor MetHb. In fact, abnormal types of haemoglobin such as MetHb can confuse a standard pulse oximeter and result in inaccurate readings of oxygenated haemoglobin. Characteristically MetHb gives an artificial reading of ~85% (82-87%) regardless of whether the true level of oxygenated is higher or lower. Therefore, it can significantly underestimate the low level of oxygen the patient is experiencing.

Specialist oximeter devices that can recognise abnormal haemoglobins such as MetHb are available. However, these are significantly more expensive than standard saturation monitors.
These specialist monitors are carried by the ambulance service Hazardous Area Response Teams (HART). These monitors are carried by these specialist ambulance response teams due to the incidents they are responded to which includes industrial accidents and chemical exposures.

The exact level of MetHb accurately measured by these monitors is variable and there is some data to suggest that levels over 15-20% become less accurate.

Therefore, using a combination of the following it is possible to make an appreciation of the likelihood of MetHb and approximation of the level of MetHb. Though this would be more challenging if other problems coexisted with the MetHb. Several other toxins and medical conditions can create a similar pattern of clinical signs and symptoms.
The factors would include:

- Likelihood of MetHb due to circumstances patient is found in; such as known ingestion of toxin likely to cause MetHb.
- Cyanosis and chocolate brown blood
- Clinical signs and symptoms suggestive of significant MetHb levels
- Oximetry readings confirming MetHb >10%

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Causes of Methaemoglobinaemia

A pathological increase in methaemoglobin levels can occur from a number of factors including genetic predisposition or drug related. Within hospital this is most commonly related to the administration of certain types of drugs as part of patient care, notably specific types of local anaesthetic. From a prehospital perspective the most common cause is ingestions of toxins, notably ingestion of [redacted] or [redacted]. This may be accidental or intentional.
There has been an increase in intentional ingestion of [redacted] and [redacted] as a form of suicide since 2015, with a peak in 2019, though these tend to be clustered. The role of online discussion groups and ordering of the substances is recognised in the literature as contributing to these peaks of incidence.

One of the key factors in the management of these deliberate suicide attempts is the fact that often very large quantities are ingested in comparison to accidental exposures. This results in very rapid high levels of MetHb making the fatality rate higher.

Treatment of Methaemoglobinaemia

The requirement for treatment of MetHb is guided by the severity of symptoms and percentage MetHb within the bloodstream. As previously described these are related, however symptoms of low levels of oxygen being delivered to the tissues are the key determinant of requirement for treatment.

The principal component of treatment is to maximise delivery of oxygen to the tissues by increasing the oxygen levels within the bloodstream. This can be achieved in several ways but key treatment for severe MetHb is to use medication to shift the iron within the haemoglobin from Fe3+ back to the normal Fe2+, thus improving the oxygen delivery to the tissues.

Simple measures such as administering high flow oxygen will help maximise the oxygen carrying capacity within the normal haemoglobin, and to a small degree encourages the shift from Fe3+ back to Fe2+. Therefore, high flow oxygen should form a key part of the clinical response.

The dosing of methylene blue is guided by clinical presentation and MetHb levels. Hence the ability to gain accurate MetHb levels is very useful in directing treatment.

The dosing guide from Toxbase is as follows:

- Severe Life-threatening Cases
    - 2mg/kg in 100ml 5% glucose over 5 minutes
- MetHb concentration > 45%
    - 2mg/kg in 100ml 5% glucose over 5 minutes
- MetHb concentration 30-45%
    - 1mg/kg in 100ml 5% glucose over 5 minutes
- MetHb concentration < 30% with hypoxic symptoms
    - 1mg/kg in 100ml 5% glucose over 5 minutes
- MetHb < 30% without hypoxic symptoms
    - Repeat MetHb level at 30 minutes and administer 1mg/kg in 100ml 5% glucose over 5 minutes if MetHb level does not reduce or if hypoxic symptoms develop.

It should be noted that 5% glucose is not part of standard ambulance fluid protocols and if an infusion is to be given over 5 minutes this should ideally be delivered by a syringe driver or fluid infuser which is not standard paramedic equipment.

The patient may also present with other signs and symptoms caused by the severe MetHb. These could include hypotension (low blood pressure) and seizures.

The first line response to hypotension would be a fluid bolus which is within the paramedic skill set.

A single, brief seizure does not require treatment, but frequent or prolonged seizures should be treated with benzodiazepines, which are within the paramedic skill set.

Methylene blue is part of antidotes carried in all Emergency Departments when incidents of MetHb occur, albeit on an infrequent basis. Plus, some medications used in hospital can precipitate MetHb formation.

Side Effects of Methylene Blue

Methylene blue is not without side effects. Severe allergic reactions appear uncommon, but this medication is rarely used to the true incidence is difficult to predict. Relatively common symptoms are headache, nausea and vomiting. Though these symptoms should be considered relatively

insignificant in the context of the sever symptoms of [redacted] poisoning and the severity of this toxicity.

One potentially significant side effect is that methylene blue may precipitate serotonin syndrome. Serotonin syndrome is when medications interact and cause the release of large amounts of serotonin within the body. Serotonin is naturally occurring chemical that transmits signals in the nervous system. The symptoms of serotonin syndrome range from mild to life-threatening.

These symptoms include tachycardia (fast pulse), hypertension (high blood pressure), flushed skin and hyperthermia (high temperature). There is also commonly agitation, tremor, increased muscle tone. This syndrome can not effectively be treated by paramedics.

The exact incidence of serotonin syndrome in those treated with methylene blue for [redacted] poisoning is unknown, however the cases that are reported in the literature are very severe. Though that may be due to the fact that only significant cases would gain publication in a peer-reviewed journal. NPIS might be able to give us additional information.

Serotonin syndrome usually occurs in those patients taking selective serotonin reuptake inhibitors. This is either because of taking excess amounts in overdose or when another medication is given that precipitates it. These are medications are very common in the management of mental health patients, so there is an increased likelihood the patient group taking [redacted] as a method of self-harm will be taking them. So, whilst this risk may be acceptable in those with proven MetHb it may not be without confirmation.

Carriage of Methylene Blue by Ambulance Service

Firstly, it is not for NARU to mandate what is carried on frontline ambulance. This would be a decision for each individual ambulance Trust and be guided by JRCALC and NASMeD. However, given the role of HART in Individual Chemical Exposure (ICE) incidents we ae keen to understand the magnitude of the situation and collaborate with experts to scope the potential benefits of this antidote being available. Though it should be recognised a HART response would not be available in a timely fashion across England to prevent deaths even if methylene blue were carried by every HART unit.

The use of methylene blue by paramedics would require significant support as it is not within the list of Schedule 17 medications under the Human Medicines Regulations 2012. Therefore, a Patient Group Directive (PGD) or verbal order from a prescribing clinician would be required for them to administer it. This would be in addition to a training package.

The dose required is 1-2mg/kg body weight and this is given in a glucose solution.

The dose required to treat a large adult (100kg) would be 100-200mg. This is a significant amount that will require storage within the ambulance. Given space is limited, we might be faced with decisions as to what would be removed from the ambulance to make room for the methylene blue. Therefore, needing to prioritise the medications carried.

As previously discussed the additional 5% glucose 100ml bags and potentially an infusion pump would be significant additional equipment costs and training burden.

The cost of a full treatment regime for a 100kg adult would be £600 to £1,500 depending on which brand were carried. Whilst this sum is insignificant for an individual life saved, if taken in the context of that amount for every frontline ambulance in England, that is a substantial outlay.

There are at least two variants of the product used within UK practice. Each would require an individual PGD to allow paramedic administration. It is not that common a medication and we would need to understand the production rate and supply chain flow. If this is a rate limiting step

this could have unforeseen consequences if the supply is directed to prehospital providers in large quantities to the detriment of hospital supply.

This then needs to be balanced against the shelf-life of the product plus the frequency of use. Particularly in the current health economic climate. This will vary according to exact product, but the shelf life appears to be relatively short. (In my Emergency Department we recently received additional stock of methylene blue as we had a cluster of [redacted] poisoning presentations. This stock had a shelf life of 8-months.

This all impacts on cost and frequency of use. This will be predicated on the incidence, which is not well defined.

Therefore, the overall cost burden of equipping every ambulance in the UK with methylene blue is likely to be very high and potentially prohibitive in the current financial situation. That is before we consider the storage space required and the training burden.

I also note the recent response from the NPIS Clinical Standards Group that is not supportive of the carriage of methylene blue on every ambulance. They remain to be convinced of the need for HART to carry this until further evidence is provided. The preliminary data below, from the WMASUFT trial has been shared with them.

Following the Prevention of Future Deaths report issued to WMASUFT in 2020 they embarked on carrying methylene blue in HART as a trial. I have recently received the interim report which gives 4 uses in the 9 cases attended over 4 years. This is equivalent to one case for every 0.5 million 999 calls. So, whilst the incidence of [redacted] poisoning is increasing it is still a very rare occurrence for front line ambulance responders. Methylene blue was administered in four of the nine cases. Three of these uses seem to be of benefit with survival to the ED.

One further administration was given in ED when the patient was conveyed in cardiac arrest and the ED stock of methylene blue could not be accessed rapidly, they did not manage to resuscitate this patient and the patient unfortunately died.

In the 5 cases when methylene blue was not administered, 4 were obviously deceased on arrival of the first attending ambulance crew.

In the remaining case, the patient gave a history of [redacted] ingestion and had mild, rather non-specific symptoms and MetHb waveform showed a non-toxic level. So, administration was appropriately withheld, and the patient conveyed to ED for formal assessment including accurate MetHb levels through blood testing.

The subject of antidotes carried by HART is on the list for discussion at a Clinical Subgroup. The advice from this group will be guided by subject matter experts in toxicology and prehospital care. Methylene blue and the detection and management of methaemoglobinaemia will be one of the topics covered. Until we understand the frequency, potential benefits and costs we will not be able to provide guidance to HART. This could be part of a wider trail across a number of HART units to collate more data on patient benefits.

However, it is still essential it is appreciated that we cannot mandate carriage of any medication, neither on every frontline ambulance, nor even enforce the carriage by every HART unit. This would be dependant on the agreement of the respective ambulance service medical directors for each HART unit.

Unfortunately, even if carriage by HART is accepted and rolled out this may not prevent every future death from nitrite-nitrate ingestion due to dose taken and time for HART to attend.

The decision as to whether to wait for HART or transfer the patient to the nearest Emergency Department, where the treatment is available, would need to be made on a case-by-case basis. It would be potentially detrimental if an ambulance crew were to wait at scene for the arrival of HART

with the antidote when this could be achieved in a timelier way by rapid conveyance to the nearest ED which will have the antidote.

Incidence of [redacted] Poisonings

A factor in our decision making will be the incidence of [redacted] poisoning. This is challenging to ascertain with accuracy within the UK. A recent literature review by Tusiewicz *et al* (Toxics 2023: 11, 832) demonstrated a significant increase in suicide attempts and deaths through [redacted] ingestion from 2015, peaking in 2020 across the world. This is reinforced by an Australasian study relating to [redacted] suicides by Stephenson *et al* (Forensic Science, Medicine and Pathology 2022: 18: 311-318). This review demonstrated 10 deaths between 2000-2019, these only began in 2017 with a steep increase to 2019. Many of the recent increase in cases are linked to ability to purchase on-line [redacted] or websites advocating [redacted] to commit suicide. Arguably, if considering the broader scope of preventing deaths then the ability to purchase [redacted] online should also be part of the solution alongside the availability of antidotes. I am aware this subject is part of another Regulation 28: Prevention of Future Death report.

There is undoubtedly an increase in [redacted] ingestion over the recent years. This has resulted in several Regulation 28: Prevention of Future Death reports relating to [redacted] poisoning. However, those are often sent to different responsible bodies by each Coroner, so neither NARU nor NHSE may be sighted on them all. [redacted] from NHSE EPRR and I have reviewed the open access judiciary website to aim to collate all the cases. Though I am not sure if additional information may be available via the Chief Coroner or via National CBRN centre.

The coronial information will give the context of those who have died as a result. In addition, we will require the incidence of [redacted] poisonings attending the ED. The NPIS actively attempt to gain data on these cases, and they request they are contacted if any cases present. This is to not only to provide support to the clinical care but facilitate audit and follow up. Therefore, they are likely to have reasonably accurate date on those that have not died at scene.

Future Direction

The forthcoming NARU Clinical Subgroup in September has [redacted] poisoning on the agenda alongside other toxicological matters. We will review the evidence from the WMASUFT trial alongside the proposed project from YAS. Ideally, we should create a unified trial across several ambulance Trust HART units to collate data from across the country.

A review of all the previous Regulation 28; Prevention of Future Death Reports can assist us.
I will be meeting with NASMeD and JRCALC on 31st July to discuss a forthcoming Coroner's inquest on another nitrite poisoning where JRCALC have been named as an Interested Party.

In conclusion I would like to express my deepest sympathies to the family of Fern for their loss. In addition, my sincere condolences to all other families who have experienced the tragedy of family member suicide due to a [redacted] ingestion.

Sincerely,

[redacted]

[redacted]MBE BSc(Hons) MBChB FRCS FRCEM DipIMC DipHEPRR

[Ends]