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MEDICO PHARMACOLOGICAL REPORT ON THE RISKS IN USE OF NALOXONE WITH PATIENTS DEPENDENT ON OPIATES FOR ANALGESIA ESPECIALLY FOR THOSE WHO HAVE CARDIAC PROBLEMS (REDACTED FOR CONFIDENTIALITY)

Prepared at the request of:
xxxxxx

In the case of:
xxxxx

Presented by

Dr Malcolm VandenBurg BSc MBBS FISMA FCP FFPM FRCP

I have produced in excess of 200 medico legal reports for criminal, civil and family courts as well as tribunals and other regulatory bodies. Instructions have been received from many solicitors and barristers for defence and prosecution, as well as CPS, Police Authorities, Independent Police Complaints Commission, Police Federation, Armed Forces, Immigration Authorities, Ministry of Defence, Royal Air Force, the Army & Medical Defence Organisations.
I have organised post graduate medical education for the Royal College of Psychiatrists, the Royal College of General Practitioners, the Royal Society of Medicine and many UK universities and health authorities.

Specialist in General Medicine, Consulting Pharmaceutical Physician

Fellow, American College of Clinical Pharmacology, 1991
Fellow, Faculty of Pharmaceutical Medicine, 1993
Fellow, Royal College of Physicians, 1996
Fellow, International Stress Management Association, 2011

BSc Upper 2nd Class Hons. Physiology 1970 (Cardio-Respiratory and Neurology)
A registered Medical Practitioner, MBBS, St Bartholomew's Hospital, 1973
Joint Committee on Higher Medical Training Certificate in General (Internal) Medicine. 1982
GMC Registration as Specialist in General Medicine. 2004

Law Society approved as Expert Witness, 2004
Registered: UK National Crime Operations Faculty, 2004
National Police Improvement Agency Expert Adviser Database 2009

Member Drug Information Association. 1984
Member American Academy of Pharmaceutical Physicians. 1993
Member International Association for Cannabinoid Medicines (IACM). 2010
Member of Drugscope. 2010
Member of Medical Council on Alcohol. 2010
Member of The British Medicinal Cannabis Register (BMCR), 2010

The Boden Memorial Award for Medicine, Haberdasher's Aske School, Elstree, 1967
Herbert Patterson Medal in Biochemistry, St Bartholomew's Hospital, 1969
BMA undergraduate Research Award, 1972

PREVIOUSLY

Lecturer in General Medicine, London Hospital Medical School
Lecturer in Clinical Pharmacology, St Bartholomew's Hospital Medical School
Honorary Senior Registrar in General Medicine, The London Hospital
Director of Clinical Research, Merck Sharpe & Dohme
Cardiovascular Clinical Investigator, Psychiatric Clinical Investigator
Clinical Research Director at Nexan – Developers of sleep apnea equipment
Co-coordinator of Positive Under Pressure Workshops for healthcare professionals
Author of Expert Reports (40) for Pharmaceutical Product Licences
200 published articles on the effects of pharmaceutical medicines & general medicine
Responsible Physician for worldwide registration of anti-hypnotics, anti-arrhythmics, antibiotics & drugs for cardiovascular disease & epilepsy, 30 papers and articles on stress
Editor in Chief: Dilemmas and Solutions in Global Drug Development – PJB Publications
Author: Good Clinical Practice for Investigators and Standard Operating Procedures for Investigators

Medical Advisor to Release (the drug assistance charity) 1973 – 1978

CONTENTS

Throughout this report, where I quote from papers supplied, this will be entered in italics, whenever I am giving my opinion throughout the body of the report; this will be typed in bold.

INTRODUCTION

1. This is a redacted version of a report I was instructed to do by xxxx who was privately funding a medico-pharmacological report into the effects of Naloxone when used to reverse opiate toxicity in patients with cardiac disease.
2. The points that I would make, by way of introduction are:
    a. Reversal of opioid respiratory depression and other effects of opioids are different when the opioid is used to therapeutically alleviate the pain of cancer compared to non-therapeutic overdose.
    b. The speed of any clinical change after the Naloxone is given may be used as evidence as to whether the clinical picture was produced by opioid toxicity.
    c. The dosing schedule is by slow titratable infusion or repeated injections and never by bolus, particularly in this group of patients, which should be particularly slowly in patients with cardiac disease, especially when severe. A dose lower than 400 microgram should probably be used and it is suggested that this could be as low as 1 microgram per kg.
    d. Pain itself may worsen coronary artery disease, and cardiac symptomatology and physiology, both acutely and chronically.
3. Of particular importance is the fact that the literature surrounding the use of Naloxone in text books, the Summary of Product Characteristics and the generality of the literature advises extreme caution when Naloxone is given to people with severe coronary artery disease.
4. As I succinctly understand it:
    a. xxxxx had advanced mesothelioma, precipitating severe pain and was on opioids to control this.
    b. xxxx also had severe coronary artery disease, with other cardiac pathology and symptoms.
    c. Her mental and physical state deteriorated, resulting in confusion, decrease in consciousness and other medical sequelae, for which no obvious cause was

found. It was thought this may be due to opioid toxicity and Naloxone was administered.

5. The Naloxone was administered in one 400 mcg bolus, and not by any method of slow titration, which would have been deleterious to XXX's health. The medical records, as I understand it, do not show that the prescribing doctor gave any thought to reducing the dose due to XXX' severe coronary artery disease.
6. There was no immediate reversal or improvement of xxxx's symptoms, indicating they were unlikely to be due to opioid toxicity.
7. No allowance or note was made for the fact XXXX had coronary artery disease.
8. Over a period of time xxxxxx was left in severe pain, which due to the sympathetic nervous system stimulation and probably cytokine release, had the potential to precipitate worsening of the cardiac anoxia, decreasing cardiac function, worsening any heart failure and may have produced arrhythmias and cardiac arrest.
9. Other ways in which severe pain and sympathetic stimulation affect the heart is to increase systemic blood pressure and resistance, and thus the work of the heart at the same time as increasing intra cardiac muscular pressure reducing blood flow and producing wall motion abnormalities.
10. There are many theories as to the mechanism of this, but one is an increase in intra cardiac myocyte calcium and intra cellular calcium overload. Systemic effects may be worsened by a redistribution of fluid within the body.
11. After three days xxxx sadly succumbed to the totality of XXX'Smedical conditions and died.
12. On review, the guidelines for the applicable Trust did not cover the dangers of Naloxone in people with coronary artery disease.

NALOXONE IN CARDIAC DISEASE

13. For my opinion, I rely on a number of publications:

Meyler's Side Effects of Drugs

14. Meyler's Side Effects of Drugs makes the point that:

'*Naloxone is an opioid antagonist devoid of pharmacological activity, except for its reversal of opioid effects.*

As Naloxone is widely believed to be innocuous, large maintenance doses of opioids are commonly used, in the belief that the reversal can be safely achieved at the end of anaesthesia.'

15. It is this belief that it is innocuous which allows doctors to use it and guidelines to recommend its use in a cavalier fashion.

16. Evidence is quoted for it producing between four to 30 serious complications per 1,000 patients with drug overdose treated for Naloxone such as asystole and pulmonary oedema

17. Regarding its use and effect on the cardiovascular system, it states that '*Doses of Naloxone over 1pg/kg* (**I think this is a misprint and should be 1µg/kg**) *should be given with caution, especially to patients with hypertension. Massive release of catecholamines in response to pain after administration of Naloxone can trigger left ventricular failure, partly by causing a shift in fluid from the intravascular to the interstitial space. Thus, alpha-blockers such as phentolamine have been postulated to be beneficial in its management. A fatal case of pulmonary edema followed the use of Naloxone in a young man, although the causal link was disputed.*

Severe hypertension and multiple atrial extra beats have been reported after administration of Naloxone, especially in patients with coronary heart disease.'

18. This supports my view that the mechanism whereby Naloxone causes cardiac side effects is due to the release of catecholamines in response to pain after administration of Naloxone.

19. It should also be noted that increasing doses of Naloxone have been associated with increasingly impaired cognitive performance. Therefore the effects on cognition are not only the reversal of opioid decrements in cognition.
20. Under the heading '*Susceptibility Factors'* it states '*Patients with pre-existing cardiac abnormalities are particularly susceptible to effects such as hypertension, pulmonary edema, atrial and ventricular dysrhythmias, and cardiac arrest, which can occur when naloxone is given to reverse opioid effects.'*
21. I attach the relevant monograph for Naloxone in Meyler's Side Effects of Drugs of drugs 2006. (Please see attached reference 1.)

Martindale

(Please see attached reference 2.)

22. Martindale, which is published by the British Pharmaceutical Society and is the standard text to which all doctors should refer, in the monograph on Naloxone, under '*Adverse Effects*', states that '*there have been individual reports of hypotension and hypertension, cardiac arrhythmias, and pulmonary oedema generally in patients given Naloxone postoperative'.* But also quotes cases in younger healthier people.
23. In '*Precautions*' it further states '*Caution is required in patients with cardiac disease or those receiving cardiotoxic drugs'.*
24. It states that the reversal effect usually occurs within two minutes and that the duration of effects is one to four hours.

Summary of Product Characteristics

25. The Summary of Product Characteristics (SPC) is a legal document drafted by the product licence holder and approved by a regulatory body. In the UK, this would be the MHRA - the Medicines and Healthcare Products Regulatory Agency.
26. We have sourced eight SPCs relating to Naloxone for the reversal of opioid symptomatology. Five are by injection.

Medicine Name	Active Ingredients/Generics	Company Name	Attachment No
Naloxone 400 micrograms/ml solution for Injection	**naloxone** hydrochloride	Hameln Pharmaceuticals Ltd	3
Naloxone 400 micrograms/ml Solution for Injection or Infusion	**naloxone** hydrochloride dihydrate	Wockhardt UK Ltd	4
Naloxone Hydrochloride Injection USP 40 micrograms/2ml	**naloxone** hydrochloride	Mercury Pharma Group	5
Naloxone Hydrochloride Injection USP 400 micrograms/1ml (0.4mg/ml, 1ml).	**naloxone** hydrochloride dihydrate	Mercury Pharma Group	6
Naloxone Hydrochloride Injection, Minijet.	**naloxone** hydrochloride dihydrate	International Medication Systems (UK) Ltd	7
Suboxone Tablets 2mg/0.5mg	**naloxone** hydrochloride dihydrate, buprenorphine hydrochloride	RB Pharmaceuticals Ltd	8
Suboxone Tablets 8mg/2mg	**naloxone** hydrochloride dihydrate, buprenorphine hydrochloride	RB Pharmaceuticals Ltd	9
Targinact 5 mg/2.5 mg, 10 mg/5 mg, 20 mg/10 mg and 40 mg/20 mg prolonged-release tablets	oxycodone hydrochloride, **naloxone** hydrochloride dihydrate	Napp Pharmaceuticals Ltd	10

Naloxone 400 micrograms/ml solution for Injection

- Hameln Pharmaceuticals Ltd

(Please see attached reference 3.)

27. The SPC by Hamlen Pharmaceuticals, in section 4.1 entitled '*Therapeutic indications'* states:

- Complete or partial reversal of CNS and especially respiratory depression, caused by natural or synthetic opioids.
- Diagnosis of suspected acute opioid overdose or intoxication.

- Complete or partial reversal of respiratory and other CNS depression in the neonate whose mothers have received opioids.

28. Section 4.2 entitled '*Posology and method of administration*' is the dosing schedule in which two clinical conditions which may have been appropriate here.

29. Firstly, is the reversal of central nervous system side effects, including respiratory depression. The dose for adults is given as:

'Dosage is determined for each patient in order to obtain optimum respiratory response while maintaining adequate analgesia. An i.v. injection of 0.1 to 0.2 mg naloxone hydrochloride (approx. 1.5-3 µg/kg) is usually sufficient. If necessary, additional i.v. injections of 0.1 mg can be administered at 2 minute intervals until satisfactory respiration and consciousness are obtained. An additional injection can again be necessary within 1 to 2 hours, depending on the type of active substance to be antagonised (short-term effect or slow release), the amount administered and time and mode of administration. Naloxone 400 micrograms/ml can alternatively be administered as an i.v. infusion.'

30. Secondly, for the diagnosis of suspected opioid overdose, the dose for adults is given as:

'The initial dose is usually 0.4-2 mg Naloxone hydrochloride i.v. If the desired improvement in the respiratory depression is not obtained immediately after i.v. administration, the injections can be repeated at intervals of 2-3 minutes. Naloxone 400 micrograms/ml can also be injected intramuscularly (initial dose usually 0.4-2 mg) if intravenous administration is not possible. If 10 mg Naloxone hydrochloride does not produce a significant improvement, this suggests that the depression is wholly or partially caused by other pathological conditions or active substances other than opioids.'

31. There is a note that in elderly patients with pre-existing cardiovascular disease it should be used in caution since serious adverse cardiovascular effects such as ventricular tachycardia and fibrillation may occur, particularly postoperatively.

32. Section 4.8 entitled 'Undesirable Effects' lists the following undesirable effects with the following frequencies:

Cardiac disorders

Common: Tachycardia

Uncommon: Arrhythmia, bradycardia

Very rare: Fibrillation, cardiac arrest

Vascular disorders

Common: Hypotension, hypertension

Hypotension, hypertension and cardiac arrhythmia (including ventricular tachycardia and fibrillation) have also occurred with the postoperative use of Naloxone hydrochloride. Adverse cardiovascular effects have occurred most frequently in postoperative patients with a pre-existing cardiovascular disease or in those receiving other drugs that produce similar adverse cardiovascular effects.

The following frequency terminology is used:

Very common:	= 1/10;
Common:	= 1/100, < 1/10;
Uncommon:	= 1/1,000, < 1/100;
Rare:	= 1/10,000, < 1/1,000;
Very rare:	= < 1/10,000;
Not known	(cannot be estimated from the available data)

Naloxone 400 micrograms/ml Solution for Injection or Infusion

- Wockhardt UK Ltd

(Please see attached reference 4.)

33. Surprisingly, this is not exactly the same as the SPC of Hameln Pharmaceuticals above, but has similar therapeutic indications and similar dosing schedules.

34. In section 4.4 entitled '*Special warnings and precautions for use'* it states '*Cautions: cardiovascular vascular disease or concomitant cardiotoxic drugs as serious adverse cardiovascular effects have been reported.'*

35. Section 4.8 entitled '*Undesirable Effects'* states these include

Cardiac disorders:

- Atrial and ventricular dysrhythmias, including atrial premature contractures
- Ventricular tachycardia
- Fibrillation
- Asystole
- Hypotension
- Hypertension
- Left ventricular failure
- Cardiac arrest

36. It also lists the psychiatric complications as:

Psychiatric disorders:

- Behavioural changes, including violent behaviour
- Nervousness
- Restlessness
- Excitement
- Irritability

Naloxone Hydrochloride Injection USP 40 micrograms/2ml

– Mercury Pharma

(Please see attached reference 5.)

37. This SPC by Mercury Pharma has similar therapeutic indications and dosing.

38. In section 4.4 entitled '*Special warnings and precautions for use'* this expands on the cardiovascular warning and states '*Naloxone hydrochloride has been reported to induce hypotension, hypertension, ventricular tachycardia, fibrillation and pulmonary oedema. These adverse effects have been observed postoperatively most often in patients who*

have cardiovascular diseases or who have used medicines with similar cardiovascular adverse effects. Although no direct causative relations have been shown, caution should be used in administering Naloxone 40 micrograms/2ml to patients with heart diseases or to patients who are taking relatively cardiotoxic drugs causing ventricular tachycardia, fibrillation and cardiac arrest (e.g. cocaine, methamphetamine, cyclic antidepressants, calcium channel blockers, beta-blockers, digoxin).'

39. In section 4.8 entitled 'Undesirable Effects' the following frequencies related to cardiac disorders it states:

Cardiac disorders

Common: Tachycardia

Uncommon: Arrhythmia, bradycardia

Very rare: Fibrillation, cardiac arrest

The following frequency terminology is used:

Very common:	≥ 1/10;
Common:	≥ 1/100, < 1/10;
Uncommon:	≥ 1/1,000, < 1/100;
Rare:	≥ 1/10,000, < 1/1,000;
Very rare:	< 1/10,000;
Not known	(cannot be estimated from the available data)

40. The other SPCs sourced are attached for completeness.

(Please see attached references 6 to 10.)

41. It should be noted that Martindale, Meyler's Side Effects of Drugs and the SPCs note the caution to be used in patients with cardiovascular disease and that severe consequences which may occur, even in the absence of cardiovascular disease.

LETTER - cardiologist

42. In his reply to specific questions the cardiologist makes no mention of the dangers of Naloxone in severe cardiac disease as outlined above.

ADULT PALLIATIVE CARE GUIDANCE (2011) 3RD EDITION

43. The Adult Palliative Care Guidance for the applicable cancer network does not mention, to my eye, Naloxone and the cautions needed in patients with cardiac disease, but does mention the slow rates of administration.
44. It therefore appears, in this case, that the applicable protocol was not followed in regard to dosing, but more importantly the guidelines themselves are deficient for not mentioning the known dangers and cautions with patients with coronary artery disease.
45. These guidelines have been recently updated, but to my eye, this deficiency has not been corrected.
46. In relation to Naloxone, it states '*be aware of return of severe pain'*, with no further warning as to the effect this may have on cardiac function.
47. It also states the aim of Naloxone is to reverse respiratory depression without compromising pain control.

HOSPITAL RECORDS

48. The relevant pages of the hospital records in relation to the admission on xxxx show that on xxx at xxx states '*Plan 1 try Naloxone 400 micrograms intravenously → no response. Though she has shown signs of being in pain.*' This indicates to me that the Naloxone caused XXX to have pain which could have worsened XX'S cardiac condition. There would appear to be evidence in some of the witness statements that both the giving of Naloxone and the avoidance of further opioids in the period of 30 hours precipitated pain throughout this time.
49. Both these factors would cause an acute deterioration in cardiac physiology and metabolism which could have continued in part until her death.

50. The effects of pain on the cardiac muscle, physiology and function should not be underestimated. From my brief reading it would appear that XXX'S respiratory depression was not severe enough to have justified the use of Naloxone for this reason. If it was being used to reverse what was thought to be effects on consciousness or to aid the diagnosis of opioid toxicity, it could be argued that a lower dose should have been given.

POST-MORTEM EXAMINATION

51. This confirms the severe coronary pathology, both grossly and microscopically, and in one conclusion states that in the pathologist's opinion the mechanisms by which ischemic heart disease caused death would be by a heart rhythm disturbance, which could have been consistent with the effects of Naloxone or episodes of pain and psychological and physiological stress.

REPORT OF PALLIATIVE EXPERT

52. The expert does not mention the dangers of Naloxone in patients with coronary artery disease pain and cardiac disease.

RESPONSE OF AN INVESTIGATOR

53. The investigator claims that their advisor did not think the post-mortem indicated a recent cardiac event.

54. Their advisors appear to have given no consideration as to the fact that stress on the heart may lead to a Takotsubo type syndrome. This syndrome does not produce any post mortem changes. Thus cardiac dysfunction during life may lead to normal cardiac post mortem findings. In the presence of coronary artery disease, there would be no additional acute post mortem changes visible.

55. It is entirely possible, if not probable, that not only may such syndromes occur in the presence of coronary artery disease, but they may indeed be more critical.

PAIN AND CARDIAC FUNCTION

56. There is a long standing belief that the pain of cardiac disease is physiologically, psychologically and therapeutically very unhelpful as it stimulates the sympathetic nervous system and precipitates worsening of the cardiac disease, both worsening hypoxia and arrhythmias and thus heart failure. That is why opioids are usually one of the earliest drugs administered. This may all lead to cardiac arrest, fatal arrhythmias or pump failure by any of the mechanisms suggested previously (please see point 8)
57. There is increasing evidence that when patients are in pain, their cardiac status is compromised due to sympathetic stimulation and cytokine release.
58. This produces a state akin to but not identical to Takotsubo Syndrome, with diminishing and abnormal cardiac function and raised cardiac enzymes in the absence of myocardial infarction.
59. The text books I quote, like me, believe that this is a condition that may be worsened by the use of Naloxone in patients with severe cardiac disease.

DIRECT & INDIRECT CARDIAC EFFECTS OF OPIOIDS

60. Another way that Naloxone may affect the heart is to reverse the direct and indirect effects of opioids. All opioids appear to reduce at least blood pressure and heart rate due to a mixture of pain relief and sedation.
61. Opioid withdrawal in the absence of Naloxone is known to reverse these changes through sympathetic stimulation and increase heart rate, blood pressure and probably other sympathetic stimulated cardiac physiological indices.
62. There is research showing that opioids reduce compliance and cause veno dilation and therefore reduce the workload of the heart. Naloxone could possibly alter this and reverse this beneficial effect.
63. There has been recent work to show that one opioid, Diamorphine, due to an effect on a specific cardiac opioid receptor, may help the heart withstand ischemic episodes and is thought to be useful in myocardial salvage.
64. I do not know if other opioids have been studied in this way.

65. It has been said that Diamorphine may have a different effect in this regard to morphine, but the situation is not clear.

SUMMARY

66. In summary, Naloxone was administered in a large bolus, without careful monitoring, without gaining advice from palliative expert consultation, which are all contrary to the Trust's 'Adult Palliative Guidelines' regarding Naloxone use.

67. The above more so because special care needs to be taken in Naloxone's administration for people who are opiate dependent and in need of opiates for pain relief. Additionally, care should be taken in those with coronary artery disease, other cardiac abnormalities such as cardiac arrhythmias including atrial fibrillation, other arrhythmias or heart failure.

68. I note the guidelines, Adult Palliative Guidance (which are based on regional guidance and not particular to the hospital), do not refer to cardiac risks of Naloxone which could be fatal, particularly in people with heart problems - a serious gap in guidelines which should be revised. At present they are not adequate to the task of informing doctors regarding prescription of this medication. If the guidelines are not added to with warnings, there will be a death precipitated by the administration of Naloxone to these people.

69. There is no doubt that if these risk factors are not taken account of in the use of Naloxone, fatalities can and will occur, as the literature shows, and so action should be taken to prevent future fatalities.

70. The mechanism of Naloxone leading to death is not clearly identified in the literature, but the most likely mechanism is massive release of catelcoamines etc. due to the pain induced and this then causing severe stress on the heart.

CONCLUSION

71. In my view Trusts need to update Naloxone guidelines to take account of the SPCs, Martindale, Meyler's Side Effects of Drugs and other clinical evidence that Naloxone

should be given very, very cautiously in small doses to patients with coronary heart disease.

72. It is highly probable that the Naloxone and lack of opioid pain relief can cause pain sufficiently to alter cardiac physiology and function acutely and that this could make a more than minimal contribution to a death if ischaemic heart disease is a cause of death.

[E N D]

STATEMENT OF TRUTH

Declaration

I confirm that insofar as the facts stated in my report are within my own knowledge I have made clear which they are and I believe them to be true, and that the opinions I have expressed represent my true and complete professional opinion.

I believe that the facts I have stated in this report are true and that the opinions I have expressed are correct.

I understand that my primary duty is to the Court both in preparing reports and in giving oral evidence.

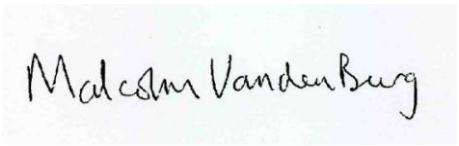
I have set out in my report what I understand from those instructing me to be the issues in respect of which my opinion as an expert is required.

I have endeavoured in preparing this report to be accurate and complete. I have included all matters, which I regard as relevant to the opinions I have expressed.

I have drawn to the attention of the Court all facts of which I am aware which might affect my opinion.

At the time of signing the report I consider it to be complete and accurate. I will notify those instructing me if for any reason I subsequently consider that the report requires correction or qualification.

This report is the evidence that I am prepared to give under oath subject to any correction or qualification I may make before swearing or affirming to its correctness.



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