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Classic cases revisited – Oxygen in court and the problem of therapeutic illusion

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Abstract

Medical science attempts to inform clinical practice. Law is concerned with causality. Intersection of law and medicine at times highlights the shortcomings in the medical approach to causality. Evidence-based medicine is only as good as the process of gathering evidence and this is inherently imperfect as suggested by philosophers. There is a risk of attributing a causal relationship when there is none, which can result in a false belief about an intervention. False beliefs can become entrenched forming a dogma. An application of treatment and a subsequent observation of clinical improvement may create a therapeutic illusion of benefit. It is possible that oxygen is used in this way. We cannot safely infer based on harm associated with its deprivation that supplementation of oxygen is beneficial in all patients. Evidence of benefit of oxygen therapy versus harm is not overwhelmingly convincing. The case of oxygen serves to illustrate a potential for a wider problem in science and medicine where potentially harmful treatments are administered based on beliefs rather than evidence and on the extrapolations from population-wide observations and without considering particulars of each case. Current application of oxygen is possibly inappropriate and efforts should be made to reappraise its use.

Keywords

Oxygen, therapeutic illusion, causality

> Scepticism is the scalpel which frees accessible truth from the dead tissue of unfounded belief and wishful thinking. The demarcation of ignorance and the exposure of folly may diminish harm, and by removing some of the rubble which impedes the way forward, accelerates progress.
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> Skrabanek P, McCormick J

> Where there is scientific activity, there is partial ignorance – the ignorance that exists as a precondition for scientific progress. And since ignorance is a precondition of progress, where there is the possibility of progress there is the possibility of error.
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> Gorovitz S, Macintyre A

Introduction

The problem of oxygen dates back perhaps to the inception of life on Earth. Nick Lane, in his book on the subject, points out that life evolved on Earth in the absence of oxygen, but it flourished in its presence in spite of apparent toxicity.[1] Without a doubt, as complex multicellular organisms, we need oxygen to survive, but excessive exposure is associated with toxicity. In a number of medical conditions, there is a relative oxygen deficiency, which we term hypoxia. It has become a matter of course, to attempt to correct this deficiency by administering oxygen. Oxygen therapy, however, has the potential for harm. The causal relationship between the recovery of patients following their illness and the administration of oxygen is not certain by any means. Could oxygen treatment be a mere therapeutic illusion, or worse, could it harm our patients? The question of causality is key in medicine, yet it is rarely examined in detail from a philosophical point of view. The case of a premature boy presented below anchors those questions by focusing on causality and interpretation of medical science. The issue of causality is very important in law, but it is also of vital interest in science and in medicine. Should oxygen therapy as practiced today be a cause for concern? Is this question representative of deeper concerns with regards to present-day science?

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The case

Martin Wilsher was born three months prematurely on the 15 December 1978.[2] At the time of his birth, he weighed only 1200 g. He was admitted to the special baby care unit at Princess Alexandra Hospital in Harlow. Thanks to the dedication and care of the hospital staff, he survived in spite of a number of crises. Unfortunately in the aftermath to his prematurity, he developed an ocular condition known as retrolental fibroplasia (RLF). This has caused him to be blind in one eye and have severely impaired vision in the other eye. It has been alleged that excess oxygen, provided to him on account of a negligently placed umbilical catheter, had been responsible for his disability. The catheter was supposed to have been placed intra-arterially but was sited in the vein providing the wrong impression about the state of oxygenation. The case raised '*a question of law as to the proper approach to issues of causation which is of great importance and of particular concern in medical negligence cases*'.[2] It is known that RLF may occur in association with other conditions that affect premature babies and which did affect the plaintiff, namely: apnoea, hypercarbia, intraventricular haemorrhage and patent ductus arteriosus. How could one therefore say with certainty that it was hyperoxia that caused the visual impairment?

The seeds of doubt

While a question about oxygen toxicity is popular with the examiners, so are the questions pertaining to oxygen delivery, oxygen flux or pre-oxygenation. The fatal effects of oxygen deprivation overshadow the less tangible and perhaps more unusual side effects associated with oxygen therapy. Seizures associated with hyperbaric oxygen or pulmonary fibrosis in those in receipt of bleomycin are rare events. Likewise, direct, free radical-mediated toxicity is rarely considered, that is unless one happens to be an anaerobic bacterium about to cause a wound infection. Oxygen is toxic to some unicellular life and this has been demonstrated in a number of trials of high risk surgery, in which a high inspired fraction of oxygen (0.8) reduced surgical site infections.[3,4] Free radicals associated with oxygen exposure are not much different from those produced by ionising radiation as has been pointed out in as early as 1954.[5] We are all aware of the potential of radiation to cause harm, yet we ignore this when employing oxygen. Oxygen also has a number of physiological effects and, in particular, it is vasoactive. At high concentrations, oxygen tends to have vasoconstrictive properties, which may contribute to conditions such as retinopathy of prematurity. The recognition of retrolental fibroplasia as a disease of prematurity had occurred in as early as 1942 and the association with the 'liberal' use of oxygen has been confirmed, in what may seem an ethically dubious study published in May 1954 in JAMA.[6] In the discussion of the published literature, already then, the authors noted that not all premature infants need oxygen even if it is of benefit to some. Paediatricians in recognition of this toxicity moved away from using oxygen to more physiological air when resuscitating newborn babies.[7] Notably, the above quoted case is not the only one to wind up in court. A number of trials performed recently[8–10] examined, amongst other things, different oxygen saturation targets employed in the resuscitation and treatment of premature babies. The targets used represented the two extremes of what was deemed an acceptable range of oxygen saturation at the time the studies were designed. A study based in the USA, the SUPPORT study,[8] precipitated a lawsuit, in which plaintiffs alleged that their children have been injured through participation in the study. Judge Karon Bowdre of the U.S. District Court for the Northern District of Alabama dismissed without a trial the lawsuit against SUPPORT investigators on the grounds of failing to show causal relationship between the trial and the alleged injuries. The debate that followed the trial and the associated judgement centred on the principles and ethics of consent, and the reader can pursue it in select references 11 and 12. The message relevant to our discussion includes uncertainties about oxygen therapy and the need for consent in both treatment and research. The aversion to acknowledge the potential for harm is a striking self-deception as highlighted by the commentators, along with the potential for creating a therapeutic illusion as far as patients are concerned.[12] The other issue of interest is that of causality, which underpinned the dismissal of the lawsuit. We read in the editorial in the *New England Journal of Medicine*:

> *The judge decided that the plaintiffs had not shown reasonable evidence that the injuries the newborns had sustained resulted from participation in the research study. She believed instead that the defendants had made a cogent case that the injuries the children had sustained 'were caused by their prematurity and other complications unrelated to SUPPORT.' There was insufficient evidence of causality to merit a jury trial, and the case was dismissed.*[13]

Paediatricians are not the only specialists to have recognised the harms of excessive oxygen use. Although it took some time, cardiologists also became aware of it. William Ganz and colleagues back in 1972 examined the effects of a high concentration of oxygen on coronary arterial flow and myocardial performance demonstrating increased coronary resistance and fall in the cardiac index.[14] The issue was examined again in 2005 in patients with stable coronary artery disease. The administration of 100% oxygen for 15 min led to a 40% increase in coronary vascular resistance and a 30% reduction in coronary blood flow.[15] Already in 1976,

a controlled trial failed to show any benefit of oxygen in uncomplicated myocardial infarction.[16] Interestingly, there were more deaths in the oxygen group (11.25% vs. 3.8%), but without reaching statistical significance. Published in 2015, the AVOID study demonstrated the harmful side of oxygen therapy showing positive correlation between oxygen administration (vs. air) in ST elevation myocardial infarction and infarct size, frequency of arrhythmias and recurrent infarction.[17,18] Finally, outcomes following cardiac arrest in patients exposed to hyperoxia appear to be worse than those who avoided it,[19,20] although not all investigators agree.[21] Outcomes in critical illness vis-a-vis oxygen are also subject to scrutiny with a suggestion of worse outcomes in association with hyperoxia[22] and have been discussed at length in this journal.[23]

Therapeutic illusion

In 2007, Caudwell Xtreme Everest expedition set out to perform a vast array of physiological experiments pertaining to hypoxia associated with sojourn to high altitude. Amongst them was arterial blood gas sampling at an altitude of 8400 m, an altitude at which ambient barometric pressure was 272 mmHg (36.3 kPa).[24] The subjects had extreme levels of hypoxaemia with mean a pO_2 of 3.28 kPa (range 2.55–3.93 kPa), yet all went on to summit Mount Everest and returned home to successful professional careers. The study suggested that mere hypoxia, even if severe (albeit with significant period of adaptation), is not enough to terminally compromise human physiology. Is hypoxia a pathology in its own right, or a merely symptom of pathology? Subhi and colleagues published an epidemiological review of hypoxaemia in children in developing countries.[25] They presented a median prevalence of hypoxaemia in pneumonia among children as 13%. They estimated that this corresponds to at least 1.5 to 2.7 million cases of hypoxaemic pneumonia presenting to health care facilities. Does it immediately mean that offering oxygen to all those children will reduce mortality? Afterall, WHO lists oxygen as an essential medicine. What might be the cause of death or morbidity in those children – hypoxia or pneumonia? A leap of faith is easy and certainly in some children oxygen therapy will be of benefit and might be life-saving, but is its administration to all of them dictated by evidence or by a belief? Would all those children benefit from oxygen and if not, which ones would? The above studies set the scene for a fundamental problem faced by science – a problem of causality. This has been a source of much debate for philosophers over the centuries. Notably, David Hume asserted that we cannot infer causation from mere observation. The problem lies in the imperfection of our ability to perceive the world. It is beautifully described, (for the less philosophically-minded) by Joseph Agassi, one of Karl Popper's students, who noted that '*we constantly read meanings into perceptions, we constantly see meaningful facts and we do not know what portion of our observation is perception and what portion of it is theorizing*'.[26] This bias occurs beside the inherent imperfection of our powers of perception. Agassi stands on the shoulders of giants when stating – '*both Sir Francis Bacon and Rene Descartes noticed that because we feed our ideas into our observations our studies are at best worthless unless they are very, very careful*'. He does examine the issue in detail offering a solution: '*we can observe ourselves observing, develop some theories of observation, and hopefully use these theories to improve our powers of observation*'.[26] He also worries about exceptions to the rule – something which we will return to later. Any disillusionment that exists with EBM has not taken on an active applicable form within science, but Agassi's suggestion might be worth considering.

Returning to the problem of oxygen, we face a quandary. Can we say with certainty that giving oxygen is of benefit to hypoxic patient? It is time perhaps to introduce the concept of therapeutic illusion. It is attributed to K B Thomas, a general practitioner who in 1978 conducted a study randomising patients with non-specific symptoms and no diagnosis to one group where no treatment was offered, and another group where a 'symptomatic diagnosis' was offered along with medication. He found no differences in outcomes between the two groups concluding that:

> *The danger is that the doctor may ascribe recovery to his treatment and go on to take this as confirmation of his diagnosis. There may thus appear to be a relationship between diagnosis, treatment, and recovery which is not true. In the past this therapeutic illusion has been responsible for many mistaken diagnoses and much useless medication.*[27]

The theme has been picked up recently by David Casarett writing in the *New England Journal of Medicine* about the efforts to reduce inappropriate use of medical treatments and diagnostics tests. He notes that:

> *The outcome of virtually all medical decisions is at least partly outside the physician's control, and random chance can encourage physicians to embrace mistaken belief about causality*.[28]

Therapeutic illusion with time and practice may evolve into dogma, often enshrined in guidelines and blessed by the experts. This occurs in the presence of biological plausibility and sometimes even evidence from a clinical trial. In critical care, this has been encountered notably in the case of glycaemic control, but other examples abound. Appendicitis is but one of them. Untreated, it leads to perforation and peritonitis and should always be managed surgically. Or

should it? Those attempting any medical examination are taught to be wary of statements beginning with the words always or never. Published in *JAMA*, the APPAC Trial has enrolled 530 adults with simple appendicitis confirmed by CT scan, randomising them to conservative management with antibiotics or surgical management by means of open appendicectomy. A successful cure was achieved in 256 of 257 (99.6%) patients undergoing surgery, but notably only 70 patients in the non-operative arm of the trial went onto having surgery in the year after presentation. The remaining 186 did not require surgery.[29] Another recent study comparing conservative and surgical management options in paediatric appendicitis concluded that conservative strategy is an effective treatment strategy for uncomplicated appendicitis and is associated with less morbidity and lower costs.[30] What might have seemed like an unshakable truth about appendicitis has been challenged quite successfully. Other than its application in hypoxaemic patients with chronic obstructive pulmonary disease,[31,32] where oxygen is used as a pulmonary vasodilator, there is little evidence to support direct impact of oxygen therapy on mortality. Are we merely attributing the benefit to oxygen or is there true benefit in all the hypoxaemic patients treated with this gas?

Free and radical thoughts?

The foundations of science we firmly believe in are not as firm as we might think. The problem of causality has long bothered philosophers, it is clearly important to lawyers, but somehow has been largely been ignored by the physicians, who enjoy hiding behind the statistical significance. Publications expressing unhappiness with the state of science are not frequent for fear of upsetting the status quo as outlined by Richard Horton, the Editor of Lancet. He begins his single page commentary with the remark – '*a lot of what is published is incorrect*'.[33] Some other established academics also bravely stick their neck out. Professor John Ioannidis recently complained about the ultimate EBM tool – the meta-analysis – as tainted by under-appreciated biases and vested interests.[34] Between the problem and the conclusion concerning oxygen therapy stands the question over the role of evidence based medicine in attributing causal relationships. Can we infer from the medical research the required causal relationships with sufficient certainty? As Richard Horton says, '*in their quest for telling a compelling story, scientists too often sculpt data to fit their preferred theory of the world. Or they retrofit hypothesis to fit their data*'.[33] Worried about culpability in cases of medical error, Gorovitz and MacIntyre proposed a theory of medical fallibility, noting a problem with the generalisability of science (all hypoxic patients are the same, all patients with pneumonia are the same, all patients with hypoxia or pneumonia should be treated with oxygen) and the failure to focus on the particulars of the case. They write: '*The Aristotelian inheritance of natural science, as a result of which natural science is defined so that it is concerned exclusively with the knowledge of universals, blinds us to the existence of particulars as proper objects of knowledge*'.[35] They also supplement the current argument about the potential harms of oxygen therapy in the following words:

> *A physician may not merely fail to cure, but may possibly damage a patient, without in any way violating the canons of impeccable practice. A common response to such outcomes is an attitude of humility in regard to the state of development of medical knowledge, but we are suggesting that what is perhaps more appropriate is humility in regard to the richness and diversity of individuals regardless of the state of medical science.*[35]

This is echoed by Joseph Agassi:

> *I say medical practice [. . .] makes allowances for reasonable errors – at times these errors cost patients their lives, yet without thereby throwing adverse light on those who make them. When is an erring practitioner culpable? This question must be clearly decidable. In democracies the rule is simple: we may declare erring practitioners culpable only when there is no reasonable doubt.*[26]

And this is the rule quite commonly adopted by the law.

Conclusions

This case highlights that causality in science is not straightforward. The problem with this conclusion is twofold. First, we risk attributing a causal relationship when there is none – for example resulting in a false belief about an intervention (therapeutic illusion), and second, most of medical science becomes suspect. Evidence-based medicine is only as good as the process of gathering evidence and this is inherently imperfect as suggested by philosophers. The evolving nature of medical knowledge is a testament to that. In the case of oxygen, the evidence of benefit versus harm is not overwhelmingly convincing. We cannot safely infer based on harm associated with its deprivation that supplementation of oxygen is beneficial in all patients. Appreciating which patients are going to benefit most from oxygen and establishing the maximum dose may well become the next scientific objective as far as this treatment is concerned. It will allow a personalised approach, acknowledging physiological diversity of our patients and reduce chances of inadvertently poisoning them. The law generally attempts to avoid ambiguity and it is strict about causality. However, in the case of Martin Wilsher, another principle has been brought forth, although not discussed in this essay – that of 'material contribution' – a

principle evoked to acknowledge the contribution of a given act or omission to the outcome. Given the recent history of critical care interventions principally aimed at reducing iatrogenic harm (less pressure, smaller tidal volumes, less fluid), it seems it is a matter of time before a question is asked about contribution of oxygen exposure to the harm suffered. Paediatricians and cardiologists are not afraid of using oxygen but they have gently moved away from indiscriminate administration of this highly reactive gas. It is perhaps time for critical care physicians to begin defining a safe dose of oxygen and see through the therapeutic illusion created by the graceful wave generated by the pulse oximetry monitor.

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