Assessing the suitability of Xenon treatment for mass use in cases of Neonatal Hypoxic Ischemic Encephalopathy

1. Abstract

Xenon has been shown to potentially have neuroprotective properties. This could mean that it could be used as a treatment pre/post brain injury. In this case we are looking at injuries where the brain is starved of oxygen whilst the baby is in the womb. There are many different aspects of suitability that determine a 'good' medication. It seems that it could be an effective and suitable treatment.

For the purpose of this essay Neonates and Neonatal will refer to anything relating to labour and immediately post labour.

2. Introduction

2.1. Neonatal Hypoxic Ischemic Encephalopathy

In Antenatal and Postnatal settings there is always a potential for complications which could affect the baby and the mother. One of these that affects the baby is a Neonatal Hypoxic Ischemic Encephalopathy (HIE), where the baby suffers damage to the brain (encephalopathy) due to a lack of oxygen (hypoxic) because of a lack of blood flow to brain tissue (Ischemic). [1] [2] This can cause many diseases associated with neuro-development such as seizure disorders like Epilepsy and Cerebral Palsy. [3] Neonatal HIE occurs in 20 of every 1000 full term deliveries, however the chances of it occurring in premature babies are much higher at 600 of every 1000. [2] There has not been an established treatment yet that has a high success rate of minimising complications, as well as having general suitability for many cases. [4]

2.2. Xenon as a neuroprotectant

Xenon is an inert noble gas that had its anaesthetic properties discovered in 1939 [5] and has had other medical uses within radiology since 1955. [6] There are many means by which neurodegeneration occurs and one way that this occurs is excitotoxicity, which is the death or damage of nerve cells due to their overstimulation because of an excess presence of a

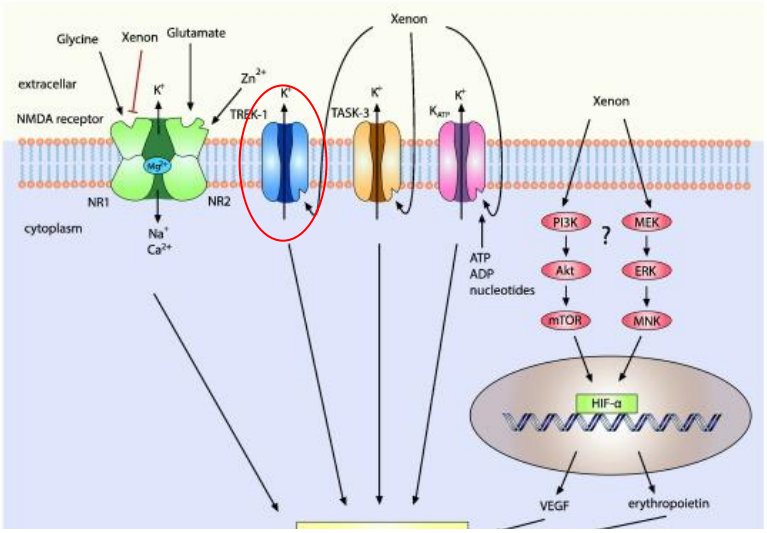

Figure 1 - figure showing the mechanisms of how xenon acts as a neuroprotectant

neurotransmitter. [7]Xenon has the ability to inhibit the overactivation of NDMA (N-methyl-D-apartate) receptors, which prevents neurodegeneration due to excitotoxicity. It also has the ability to open pathways such as TREK-1 pathways, shown (circled) in Figure 1 along with the other mechanisms of neuroprotection, which prevents neuro-inflammation. Opening the TREK-1 pathways is shown to have an effect on the levels of neurotransmitters, so has a similar end result to the protection of cells as in the inhibition of NMDA receptor mechanism. [8] Xenon also has the potential to be neurorestorative and therefore has the possibility of being used post damage event. [9] There have been a number of investigations into this theory within in vitro settings, that support Xenon acting through the inhibition of NDMA receptors. [10] [11] This is also backed up by computer simulations done at the University of Pittsburgh. [12]

3. Suitability

3.1. Ease of administration and induction speed

The ability to deliver medication to the needed recipient quickly and efficiently is key to the prognosis of the patient. Xenon, being an inhalational anaesthetic, would often be delivered by face mask or tracheal tube. However simply using these methods would not be economically viable due to the lost Xenon and its high cost, see **3.6**. You would need to use a closed delivery system that recycles the Xenon from exhaled gases. There have been multiple systems that recycle the exhaled Xenon, whilst also maintaining the gaseous concentration of the Xenon to keep treatment controlled and effective. [13] [14]

Xenon takes a relatively short time to anaesthetize a patient, with a study concluding that it achieves the anaesthetic effect in 90 seconds. [15] This can be explained by its low blood gas partition co-efficient of 0.14 (compared to Isoflurane 1.4 which is a commonly used anaesthetic). [16] [17] The lower the blood gas partition coefficient the more rapid the induction of anaesthetic effects. This is because this co-efficient describes how a gas will split between the blood and the alveoli concentration when equilibrium is reached. A gas with a lower blood gas co-efficient will require a lower uptake of gas and therefore induction of effects will be quicker. Most hospitals would be able to use the infrastructure they have already to administer Xenon due to it's inert nature.

3.2. Placental Transfer

Ideally, drugs being delivered to neonates would be administered through the mother during labour, especially when they are inhalational gases like Xenon. This is also only possible if the drug has minimal or no side effects for the mother, see **3.4.** All inhalational drugs are able to cross the placenta through diffusion. As long as the agent is able to get into the mother's blood stream placental transfer of that agent can occur. [18] [19] As Xenon and other Noble Gases are volatile, [20]they are able to cross the placental barrier rapidly due to being highly lipid soluble. This induces anaesthetic effects on the neonate quickly and also means the effects can wear off quickly after treatment conclusion. The effects need to be induced quickly because of the characteristics of an oxygen deprivation injury being very time sensitive.

3.3. BBB Transfer

Another important factor that needs to be taken into account when assessing the suitability of a drug being used to treat anything within the Central Nervous system (CNS) is whether it is able to cross the Blood-Brain Barrier (BBB). The BBB is a dense layer of mainly Endothelial and Mural cells that form a protective barrier between the brain's blood supply and the brain tissue. [21] [22] This barrier carefully regulates the movement of certain ions, molecules and cells between the Central Nervous System and the blood vessels that supply it. [22] The aim of this controlled system of transport is to keep the brain healthy and toxin free. However, in cases when the CNS requires an agent to reach its tissue for treatment of a disease or injury, the BBB becomes a limitation for what drugs can be effective.

Xenon has been shown to have had anaesthetic effects for a while now and therefore we can have confidence that it passes through the BBB. It induces the effects rapidly and emergence from the anaesthetic effect is also fast - quicker than common anaesthetics like isoflurane and nitrous oxide. [16] Xenon is a small and non-polar molecule which means it can diffuse easily across the membrane. Xenon, like Oxygen, can avoid transporters that efflux them back into the blood. This is the route that is most likely to be the way that Xenon reaches the CNS. However, there is another theory that it could pass through a nasal route, when inhaled, along the olfactory and trigeminal nerve in an anterograde way. This mechanism would skip out the BBB altogether. This is only likely in drugs with a low molecular weight like Xenon, so this could be possible. [23]

This is based on knowledge of the BBB in adults, as knowledge of the neonatal BBB is limited. There have been suggestions that younger BBBs are more permeable meaning this would not cause a problem. And with oxygen deprivation injuries in adults the BBB becomes more permeable, making it easier for more drugs to pass through. However some research has suggested the neonatal BBB reacts oppositely and becomes slightly less permeable. [24] Despite this suggestion it is likely that due to Xenon's ability to pass through the BBB so easily in normal situations, even if it was slightly less permeable I believe it would still be able to pass through efficiently.

3.4. Side effects

Even if a drug is highly effective at treating the intended problem, if it has dangerous side effects it may not be suitable overall. In pre-birth cases there is also a special consideration as the intended recipient of the treatment is the neonate but the drug is often delivered through the mother so effects can occur for her as well.

In neonates there have been no indications of any significant side effects in studies. Importantly, in a study done on neonatal piglets no Neuro or Cardio damage was seen. [25] Especially with drugs being used to treat the young there is emphasis on preventing any developmental side effects, or teratogenic effects. Studies have shown that Xenon has none of these effects. [26] [27]

For the mother Xenon also does not seem to cause adverse effects. It does not seem to cause significant Cardio or Neuro complications. Nor does it cause psychotic effects like other similar drugs. It does not irritate airways and does not seem to have many interactions with other drugs, due to its inert nature. [28] [29] It seems to slow the respiratory rate but increase tidal volume so these counter each other out, meaning the overall effect is minimal and not dangerous. [30]

3.5. Success of treatment

Xenon treatment can be used in two scenarios when dealing with Neonatal HIE. It can be given during labour, the main focus of this essay, but also after delivery to the baby directly. There have been a number of studies demonstrating the benefit of the treatment. One study by Nicola J Robertson et al looked at a number of different neuroprotective treatments that could be used on new-born infants, such as melatonin. It used a scoring system to rank different treatments on different aspects of their suitability. It gave

Xenon a 7/10 score antenatally and 8/10 for postnatal treatment in the benefit section, this gave it the second highest and highest score respectively. This study used lots of different evidence such as in vitro and in vivo investigations. [31] It has the ability to be a preconditioner as well as a post incident treatment due to its action on the m-tor pathway, a pathway that regulates a cell's life cycle. [32] [33] There have also been other studies done on Xenon's organoprotective properties in other organs such as the kidney. These are similar and relevant as they are also in hypoxia induced injury and show benefits to Xenon being used over current alternatives. [34]

Also one of the problems with HIE is the occurrence of seizures and the development of a seizure related disease, such as epilepsy. Therefore, it is beneficial that Xenon has been shown to have anti-seizure properties. It reduced neurodegeneration occurred after seizures as well as minimising the severity of the seizure. [35]

However there has been an incidence where Xenon was shown to have neither a beneficial, nor detrimental, effect on new-born rats. [36] This study seemed to only look at one biomarker and there was no difference in the presence of this biomarker between the Xenon group and the control group. We do know that there are many mechanisms of injury and therefore many ways to measure injury to the brain. So despite this study proving no significant benefit I believe that due to the large number of positive studies that we can still confidently say that it likely to be beneficial. Yet, it is interesting for researchers and would be something to look into as what other drugs may have a beneficial impact on this mechanism of injury.

3.6. Cost

The ability for a drug to be used widely heavily relies on the cost of treatment. Even if a drug is very successful in treatment if it is not economically viable for the majority of recipients it becomes a drug for the 1%. This poses ethical problems with the drug, especially when at the moment there does not seem to be alternatives for neonatal HIE. This is a problem for Xenon as it is expensive. It costs nearly seven times the amount of other anaesthetics such as isoflurane. [37] Xenon needs to be extracted from the atmosphere using a air liquification method and then a high purity of Xenon can be attained. It is an extremely rare gas which poses problems in gaining enough gas to be used within anaesthesiology in a widespread manner. Production of Xenon has gone up in recent years but so has the demand due to other industries like the aerospace industry. [38] It costs about £7 per litre, which is high compared to other volatile gases. [39]

The way around this, as suggested in **3.1**, is to use a recycling method within a closed system. The reason why cost could be so high is that not all Xenon will be used by the patient and there will be a lot escaping back into the atmosphere. So more Xenon needs to be used in order to keep up the desired concentration. If recycled less Xenon needs to be used in total to keep up optimum levels of the gas. There have been a number of systems that have been used to scavenge for Xenon in exhaled gases, such as in figure 2. [40] Using these systems Xenon treatment seems more viable and cost effective. This means it could have the same availability to patients as other common anaesthetics.

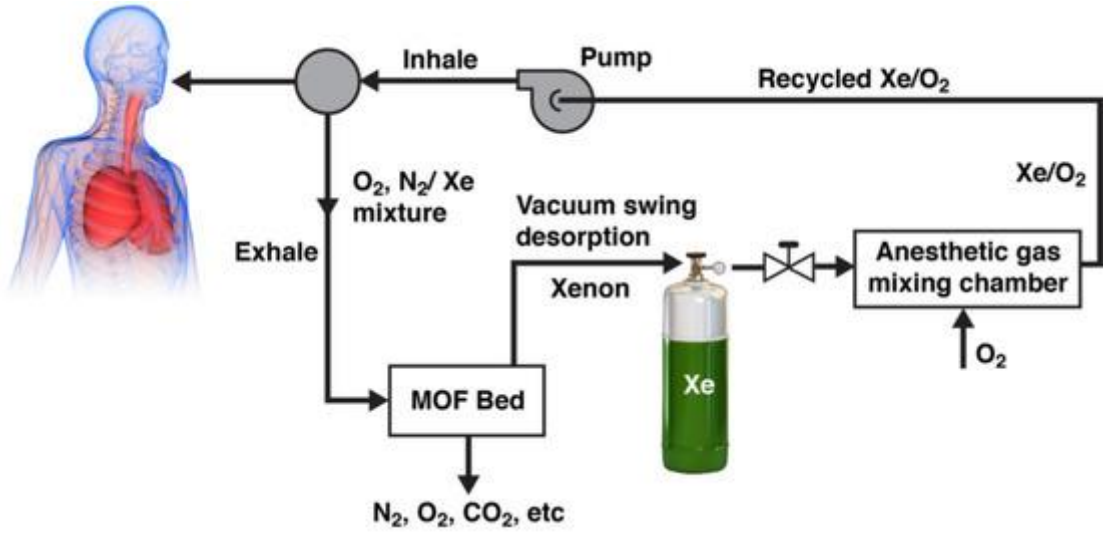

Figure 2 - figure demonstrating a Xenon recycling system.

3.7. Use in conjunction with other treatments

Xenon is often thought as a treatment that can be used in conjunction with Therapeutic Hypothermia (TH). This is a treatment where the Neonate's internal body temperature is cooled to about 33 degrees Celsius. This slows metabolism and limits damage occurring in the brain. [41] There have been mixed results in studies. A 2018 study by Ruegger et al suggested there was no reduced morbidity with this conjoined treatment. [42] However another in vitro and in vivo study was more promising showing that Xenon and TH showed significant improvements. [43]

4. Conclusion

4.1. Summary

Xenon is easy to administer and has a rapid onset of effects for the baby. Xenon can cross the placental and Blood-Brain Barrier due to its properties such as being lipophilic. It has minimal side effects for the mother and the baby, with it seeming to have benefits to the outcome of the neonate. It is

expensive but with a recycling system to prevent the exhaled Xenon escaping then it could be economically viable. Its ability to be used with other treatments is still un-known.

4.2. Verdict

A new drug, before entering general circulation, requires a lot of testing and a high level of confidence in its suitability. It appears to me that Xenon is a promising treatment for Neonatal HIE, and on paper has a high level of suitability, however it would require more data on studies done on humans. There have been plenty of instances where drugs have ticked all the prior boxes, such as working in in vitro settings as well as in animal testing, yet have not been successful in human trials. Xenon has yet to enter the second stage of clinical trials (phase 1) and has therefore only been tested on a few small select cases where the probability of a positive outcome is high. There needs to be trials involving a large number of patients that have different circumstances. If the trials are successful on these large varied groups then we would be able to be confident on it's ability to treat the majority of cases, rather then a select few that have to have certain conditions. This would make it available for mass use.

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