The Clinical Utilization of Inhaled Pulmonary Vasodilators

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Abstract
Inhaled Nitric Oxide (INO) and other inhaled pulmonary vasodilators, like Flolan, have demonstrated positive physiological responses in select patients; however, there are no clinical studies that have demonstrated any long term outcome benefits in mortality and morbidity. Because of this, their use is somewhat controversial. Still, INO and Flolan are commonly used as rescue therapy in various clinical situations. Currently, Lehigh Valley Health Network (LVHN) utilizes both drugs and has a titration protocol for Flolan, but not for INO. A retrospective analysis of 158 patients was performed in order to determine if the administration of inhaled pulmonary vasodilators at LVHN is warranted and being performed correctly. It was found that these drugs are being used for the correct clinical indications and that a majority of patients have positive physiological responses to these drugs (74.2% of those treated with Flolan and 52.9% of those treated with INO). The weaning protocol for Flolan was only carried out in 58% of the cases observed. Based on these findings it would be advantageous to LVHN and their patients for both financially and clinically to follow the Flolan weaning protocol more often and to implement a similar methodology for INO.

Introduction
While Nitric Oxide was originally described for its toxic effects back in the 18th century, it is now commonly used in the clinical arena for the treatment of refractory hypoxia, pulmonary hypertension, and unstable hemodynamics. Although the only FDA approved clinical indication is for neonates with hypoxic respiratory failure, INO is currently being used for many off-label indications in adult patients[1]. INO has demonstrated selective pulmonary vasodilation and, therefore, can improve oxygenation by shunting blood flow from collapsed or injured alveoli to healthy alveoli. Although INO can be an effective treatment, it is also an expensive one which costs about $100/hr to run and costs many institutions over a million dollars a year[2]. Due to its high cost, some institutions are seeking the use of alternative pulmonary vasodilators such as inhaled prostacyclin. One such inhaled prostacyclin is Flolan. While positive physiologic responses are well documented for both Flolan and INO, their use remains controversial because there is no significant evidence that either improves patient outcomes[3]. Still, INO and Flolan are commonly administered as rescue therapy in order to stabilize critically ill patients until a more definitive treatment can be implemented and future direction of care can be discussed with the family.

Nitric oxide causes selective pulmonary vasodilation by binding and activating soluble guanylyl cyclase, which then activates cyclic guanosine 3' 5' monophosphate dependent protein kinase (cGKI). Activated cGKI causes decreased intracellular calcium concentration and sensitivity reduction of myosin to calcium, which ultimately results in arteriolar smooth muscle relaxation[4].

Flolan, also known as Epoprostenol and PGI2, is a member of a group of physiologically active lipid compounds known as prostaglandins. Prostaglandins are derived from arachidonic acid and naturally mediate various responses to pathogens, including inflammation[5]. Specifically, Flolan causes direct vasodilation of pulmonary and systemic arterial vascular beds and inhibits platelet aggregation. Flolan works by binding prostacyclin receptors on platelets and endothelial cells. Once these receptors are activated they signal adenylyl cyclase to produce cAMP which goes on to inhibit platelet activation and activate protein kinase A (PKA). PKA inhibits myosin light-chain kinase which leads to smooth muscle relaxation and finally results in vasodialation[6].

In order to determine if LVHN is correctly administering inhaled pulmonary vasodilators as well as to observe if these therapies are effective, a retrospective analysis of 158 patients was performed. The purpose of this study is to decide if the use of inhaled pulmonary vasodilators is warranted and, if so, to make suggestions for future admiration of these therapies based on the evidence gathered.

Methodology

A retrospective chart analysis of 158 patients who received either Flolan (124 patients) or INO (34 patients) at Lehigh Valley Health Network was conducted. The clinical indication, clinical response, and total drug administration time was recorded. For the patients treated with Flolan it was noted if the prescribed titration protocol was followed. The clinical indication was recorded as one of the following: (1) hypoxia, (2) pulmonary hypertension, or (3) unstable hemodynamics. The clinical response was recorded as a positive response, neutral response, or unknown. A positive response was recorded if one or more of the following were observed during treatment: an overall increase of 2% in SpO2, a 20% increase in P/F ratio, an overall reduction of 10% in FiO2, a sustained 15% reduction in Mean Pulmonary Artery Pressure (MPAP), or if hemodynamic support was reduced. A neutral response was recorded if none of the above changes were seen. An unknown response was recorded if the changes could not be determined to be due to treatment with either Flolan or INO. Once all of the information was recorded, the data was analyzed in order to determine the results of the study.

Results

All of the observed patients were treated for a clinically acceptable indication (hypoxia, pulmonary hypertension, or hemodynamic instability). Of the 124 patents treated with Flolan, 92 (74.2%) of patents had a positive response, 26 (21%) had a neutral response, and 6 (4.8%) had an unknown response. The clinical indications for patients treated with Flolan were as follows: 54 (43.5%) were treated for Hypoxia, 24 (19.4%) for hemodynamic instability, and 46 (37.1%) for pulmonary hypertension. The mean time patents were treated with Flolan was 82.5 hours, the median time was 41.5 hours, and the range was 0.75 hours to 663.2 hours. Because the average hours on Flolan were inflated due to outliers (data that fell greater than 2 standard deviations above the average) in the data, they were also calculated without them. The adjusted mean was 61.9 hours and the adjusted median was 39.6. The Flolan titration protocol was followed for 72 (58%) of the patients treated.

Of the 34 patients treated with INO, 18 (52.9%) had a positive response, 15 (44.1%) had a neutral response, and 1 (2.9%) had an unknown response. The clinical indications for patients treated with INO were as follows: 27 patients (79.4%) were treated for hypoxia, 1 (2.9%) was treated for hemodynamic instability, and 6 (17.6%) were treated for pulmonary hypertension. The mean time that the patents were on INO was 37.5 hours, the median time was 25.8 hours, and the range was 2.3 hours to 162.9 hours. Pertinent data for both Flolan and INO is summarized in the table below.

	Flolan	INO
Positive Response	74.2%	52.9%
Neutral Response	21%	44.1%
Unknown Response	4.8%	2.9%
Percent of time protocol followed	58%	N/A
Mean time on drug	82.5 hours Adjusted: 61.9 hours	37.5 hours
Median time on drug	41.5 hours Adjusted: 39.6 hours	25.8 hours
Range of hours	0.75 – 663.2 hours	2.3 – 162.9 hours

Figure 1: Response rates, protocol, and time summaries for INO and Flolan. The "adjusted" times for Flolan are the mean and median times calculated without data that fell two standard deviations above the mean.

Discussion

The results provide some insight into how patients are currently being treated with inhaled pulmonary vasodilators and how they can better be treated in the future. According to the data, Flolan and INO are being used correctly and effectively at LVHN, although there is opportunity for improvement. Of the 158 patients observed, all were treated for one of the three approved indications and the majority of patients had a positive response to the treatment (74.2% for Flolan and 52.9% for INO). Remember that these drugs are rescue therapies and if administering them allows over 50% of patients to survive longer, their use should be warranted due to the risk/benefit profile. Consider this is in contrast with other therapies where a 50% positive response rate may not be warranted because the risk of the therapy greatly outweighs the potential benefit.

While the positive response rate recorded warrants the use of these therapies, the protocol for Flolan was only followed about half of the time it was used (58%). This may be due to a lack of priority given to the protocol by the respiratory therapists, lack of education about the protocol, or direct orders by a physician to override the protocol. Regardless of the source, the titration protocol is an important aspect of the administration of Flolan and it should be followed. The protocol is in place to ensure that patients do not react adversely to a sudden discontinuation of the drug and to ensure that the lowest effective dose is administered (which minimizes costs and potential side effects). For example, a previous study has shown that the implementation of an INO protocol reduces the direct cost associated with its use without a significant change in patient outcomes[2]. Therefore, because the titration protocols benefit the patient and institution both clinically and financially, steps should be made to make certain the Flolan protocol is followed. Furthermore, a protocol for INO should be implemented.

One final piece of information that can be gleaned from the results is that Flolan had a positive response rate about 20% higher than INO (74.2% for Flolan vs. 52.9% for INO); although, it is possible that the small sample size for INO may contribute to this observation. Still, Flolan is a much more affordable therapy than INO and long term use of INO has been associated with methemoglobinemia and increased bleeding risk[2]. With all these facts in mind, Flolan should be used to treat patients preferentially over INO. While there are situations where INO must be used, such as when a patient is on volumetric diffusive respiration (VDR), Flolan should be used when possible in order to better treat the patient and reduce the cost of care.

Conclusion

The objective of this study was to observe if inhaled pulmonary vasodilators were being administered correctly, to discover if the treatment was effective and, based on these results, to make observations and suggestions about their use. Grounded on the retrospective analysis of 158 patents at LVHN, the use of pulmonary vasodilators as a rescue therapy is warranted and they are being administered for the correct clinical indications. It should be noted, however, that the patients being analyzed were on a multitude of therapies aimed at improving the very same indications in question. For example, it proved difficult to assess whether a patient's improvement in oxygenation was due to the initiation of Flolan, a change in the Extracorporeal Membrane Oxygenation (ECMO) settings, a change in one of the many vasopressors, or quite possibly a synergistic effect of all therapies being utilized. Therefore, the results should be viewed with a healthy dose of skepticism while keeping in mind that there were patients who clearly showed a direct positive response to Flolan and INO.

So, while the use of Flolan and INO is warranted according to this study, steps should be taken within LVHN to preferentially use Flolan over INO, follow the Flolan protocol more closely, and

implement a titration protocol for INO. By doing this the institution may reduce costs, improve clinical outcomes, and increase the effectiveness of inhaled pulmonary vasodilators.

References

Walsh, Brian K., Retting, Jordan S. (2015). Implementation of an Inhaled Nitric Oxide Protocol: A Paradox or the Perfect Pair? *Respiratory Care* 60(5), 760-761. Print.
Tzanetos, Todd R., *et. al.* (2015). Implementation of an Inhaled Nitric Oxide Protocol Decreases Direct Cost Associated With Its Use. *Respiratory Care* 60(5), 644-649. Print.
Siobal, Mark S., Hess, Dean R. (2010). Are Inhaled Vasodilators Useful in Acute Lung Injury and Acute Respiratory Distress Syndrome? *Respiratory Care* 55(2), 144-154. Print.
Griffiths, Mark J.D., and Timothy W. Evans. (2005). Inhaled Nitric Oxide Therapy in Adults. *New England Journal of Medicine* 353, 2683-695.
Ricciotti, E., and FitzGerald, G. A. (2011). Prostaglandins and Inflammation. *Arteriosclerosis, Thrombosis, and Vascular Biology*, *31*(5), 986–1000. doi:10.1161/ATVBAHA.110.207449
"Epoprostenol." *DrugBank*. N.p., 13 June 2005. Web. 07 July 2015.
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