

Effects of the ongoing pandemic on Bupivacaine HCl supply

In March of 2020, the World Health Organization designated the coronavirus SARS-CoV-2, which causes the COVID-19 infectious disease, to be a global pandemic (WHO, 2020). Symptoms of the virus vary to include fever, cough, sore throat, and severe respiratory alignments, while some who catch the virus remain asymptomatic. As individuals continue to get critically ill, waves of lockdowns across the globe have hindered drug suppliers in multiple ways. Not only have certain requirement for drugs surpassed the supply capacity, but trade restrictions and logistical complications have made access to certain critical ingredients and drug products limited or impossible.

Throughout the pandemic, painkiller and sedative demands has spiked. Demand for Bupivacaine HCl, a powerful analgesic and anesthetic medicine, has dramatically increased. As global authorities work to fill gaps, drug manufacturers and contract manufacturing and developing organizations (CDMOs), such as Cambrex, have become critical in the efforts to stabilize the supply of Bupivacaine HCl and other essential drugs.

Introduction

Authorities like the United States Food and Drug Administration (US FDA) define the shortage of a medical drug as the demand or requirement for a particular drug surpassing the resources and provision of that drug. Shortages are traditionally due to suppliers exiting the business, delays in production units or manufacturing areas, difficulties obtaining raw materials or supply chains gaps including logistical issues.

A drug shortage crisis in 2011 led to the shortage of around 250 drugs in the US. In 2014, experts from the US FDA noted that “to truly eradicate or minimize the occurrence of supply interruptions and/or drug shortages, manufacturers must not only comply with good manufacturing practices, but also must invest in modernizing and/or improving manufacturing quality systems”. The idea was to encourage advanced manufacturing approaches that enabled faster, more efficient drug production, while increasing manufacturing capacity to avoid shortages (Fox ER S. B., 2014).

Later in 2018, when the problem was remaining an issue, the FDA formed the Drug Shortages Task Force to further explore the causes and come up with apt solutions. However, by 2019 the FDA announced a discontinuation of 180 drug products and highlighted a shortage of approximately 270 drug products (Shuman A, 2020).



Magnus Claesson
Plant Manager

Why Cambrex?

Cambrex Karlskoga, Sweden is the manufacturing site where Bupivacaine was first discovered in the 1950s.

Cambrex is responsible for the evolving manufacture, control and release of the drug substance.

About Cambrex

Cambrex is a leading global contract development and manufacturing organization (CDMO) that provides drug substance, drug product, and analytical services across the entire drug lifecycle.

With over 40 years of experience and a growing team of over 2,200 experts servicing global clients from North America and Europe, Cambrex is a trusted partner in branded and generic markets for API and finished dosage form development and manufacturing.

COVID-19 Exacerbates Supply Issues

The COVID-19 pandemic has further weakened the drug supply chain as demand has increased for prescription medicines and over-the-counter drugs (Arain S, 2020). Initially reported from Wuhan, China in December of 2019, by March of 2020, COVID-19 was labeled a pandemic, and compelled international authorities to take unprecedented measures including lockdowns and travel restrictions. Trade disruptions and a subsequent economic crisis at global scale ensued, which almost immediately started to adversely affect the supply chains of medical drugs and equipment (Liu S, 2020). While poorer countries like Kenya were initially the most affected by this scenario, economically stable countries have also felt the impact of the crisis (Kameri-Mbote P, 2020).

Drug substance and product supply chains are complex in nature making creative solutions necessary to overcome the challenges faced. The suitable provision of protective and therapeutic medicines, and the presence of apt medical care is necessary to assist and improve public health during the ongoing pandemic. The American Society of Health System Pharmacists has clearly given the guidelines to counter such a situation and these guidelines are being followed around the world (Pharmacists, 2020).

An Overview of Bupivacaine HCl

Bupivacaine HCl (Figure 1) is a locally acting drug that alters sodium and calcium binding in the cell membrane, leading to a change in the configuration of the membrane (NIH, 2020). This phenomena results in anesthetic and analgesic effects by blocking the generation of nerve impulses and their subsequent transmission.

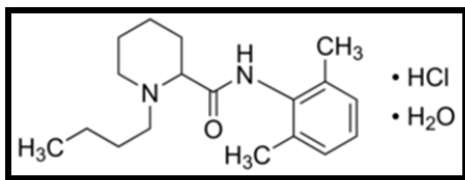


Figure 1: Chemical structure of Bupivacaine HCl

Clinically this drug is used as an anesthetic option during operations and as a pain reliever post-operation. It can be used as a safe caudal epidural block technique that is proven safe to both the mother and the child in births, as well as in other surgical anesthesia applications like abdominal and thoracic surgeries. It is also a tool of choice for pain management in dental surgeries, and in non-surgical situations, Bupivacaine HCl can be used for reducing chronic pain (NIH, 2020).

Routes for administration and required concentrations of Bupivacaine HCl are illustrated in Figure 2.

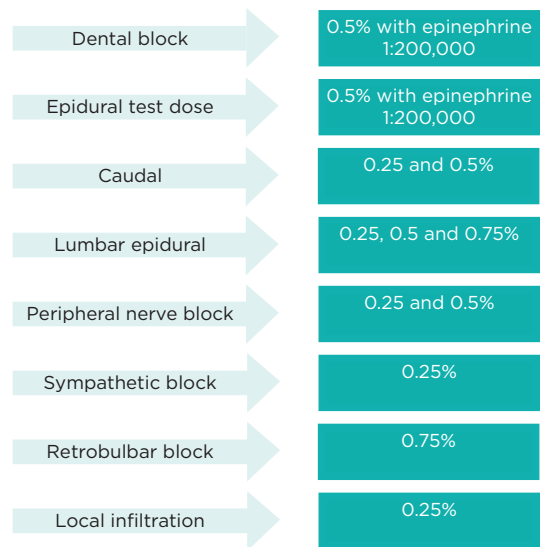


Figure 2: Routes for administration and required concentrations of Bupivacaine HCl

Bupivacaine HCl Demand Spikes

In 2018, the FDA reported a shortage of Bupivacaine HCl (FDA, 2018). The shortage raised concerns for patient safety due to unsuitable or inappropriate dosages or substitutions, and deficiency of therapeutically suitable drug programs.

A report published in 2019 recognized two main causes of the drug shortage as negligible market motivations based on low returns and quality control maintenance issues (Kasson B, 2018). Stringent laws and regulations further complicated the situation after the supply disruption.

By 2020, the COVID-19 pandemic exacerbated the issue as an abrupt surge in critically sick individuals led to the utilization of several drugs in a greater quantity, thereby depleting resources quicker than expected. Analgesics and generic sedative resource demand has grown.

Looking for a Plausible Solution

While producers normally have safety stocks to offer an uninterrupted supply during times of increased demand, this has not been enough to support the spike in demand for Bupivacaine HCl. Strategies to avoid serious drug shortages can include relaxing restrictions and exploring substitute pharmacotherapy opportunities, wherever possible (Fox ER M. M., 2018). A secondary solution of importing or exporting stock from partners to fulfill a shortage in a particular region has not been possible with an ongoing pandemic. More creative measures are needed to find a solution.

And while a logical solution may seem to be increasing manufacturing capacity, it is not that simple. Bringing a new manufacturing facility online is extremely costly and time and resource consuming. There is also a great

deal of cost and complexity to repurposing a current manufacturing facility or unit, which could ultimately lead to shortages of other drugs.

Aligning to Create New Solutions

This situation necessitates that drug manufacturers join hands with authorities to fulfill the upsurge in demands. Timely information exchanges to and from the manufacturers and suppliers can help to establish expectations that pharmacies and pharmacists can follow to improvise effective treatment plans.

Work can be done remotely where possible to curb individual to individual infection transfer and the patient population should be educated about existing options. Where feasible, manufacturers should maintain distribution, transport and storage for clinically significant drugs and actively communicate with distributors to appropriately allocate upcoming product shipments.

Pharmacies should be able to easily access availability status, in addition to having emergency ordering options and the ability to create reserve stocks in preparation of a putative second wave of this disease. Authorities should be prepared to release important medicines from reserves, which can be facilitated by deeper collaboration between healthcare establishments and advocacy groups.

Whenever additional medicines attainment is instituted, the suppliers must keep a record of the daily sales, production and demand. They must be fully aware of closed patient care areas that have lesser requirement and higher supplies of drugs already present, so that these can be redistributed to areas where they are more in demand.

Current knowledge suggests that around 12 companies in seven different countries, including China and India, manufacture Bupivacaine HCl. However, manufacturers based in India and China face significant regulatory and delivery issues due to the pandemic.

Conclusion

The recent pandemic has exacerbated existing drug product shortages and led to new shortages of drugs due to a rise in demand. Authorities are rapidly working to make decisions of where there is flexibility in drug production regulations, and to find new alternatives.

Author



Hamid Parsa, Global Sales Director,
Proprietary products

References

- Arain S, T. R. (2020). COVID-19 pandemic: Response plan by the Johns Hopkins Aramco Healthcare inpatient pharmacy department. *Research in Social and Administrative Pharmacy*.
- FDA, U. (2018, February 20). Current and Resolved Drug Shortages and Discontinuations Reported to FDA. Retrieved from US Food and Drug Administration, FDA Drug Shortages: https://www.accessdata.fda.gov/scripts/drugshortages/dsp_ActiveIngredientDetails.cfm?AI=Bupivacaine+Hydrochloride+Injection%2C+USP&st=c&tab=tabs-4&panels=1
- Fox ER, M. M. (2018). ASHP guidelines on managing drug product shortages . *American Journal of Health-System Pharmacy* , 1742-1750.
- Fox ER, S. B. (2014). Drug shortages: a complex health care crisis. *Mayo Clinic Proceedings*, Elsevier, 361-373.
- Kameri-Mbote P, K. D. (2020). Human Rights Implications of the Covid-19 Pandemic in Kenya.
- Kasson B, H. C. (2018). Considerations for management of bupivacaine formulation shortage affecting obstetric anesthesia services. *AANA Journal Online Content*.
- Liu S, L. P. (2020). Providing pharmacy services during the coronavirus pandemic. *International Journal of Clinical Pharmacy*.
- NIH. (2020, October 19). US National Library of Medicine. Retrieved from DAILYMED: <https://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=6e7fe2ee-5ee5-40a0-8644-9999032ac716>
- Pharmacists, A. S. (2020). Guidelines and Tools. Retrieved from <https://www.ashp.org/Drug-Shortages/Shortage-Resources/Guidelines-and-Tools>
- Shalini Shah M, S. D. (2020). The technological impact of COVID-19 on the future of education and health care delivery. *Pain physician*, pp. S367-S80.
- Shuman A, U. Y. (2020, April 25). Drug shortages: The view across an ocean. *The Oncologist*, p. 274.
- WHO. (2020, March 11). WHO Director-General's Opening Remarks at the COVID-19 Briefing. Retrieved from World Health Organization: <https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020>