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Brief Review

Lidocaine - Pharmacological Options Beyond Local Anaesthetic!

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Introduction

Off label prescription of pharmacological agents are common in clinical practice. Subsequently some of these drugs are recognized on a regular basis. Unanticipated pharmacological actions are noticed either in the evolution phase of drug or following some interesting observations reported during clinical practice. One such agent of interest to anaesthesiologists is Lidocaine. Multiple possible therapeutic options of this agent are now critically elucidated. Anaesthesiologists are familiar with lidocaine's potency to blunt airway irritability and cardiac arrhythmias. Interestingly its roles as antitumor agent as well as possible antibacterial and antiviral are now increasingly explored. The following text is a brief description of lidocaine's established and emerging roles other than of a local anaesthetic.

As bronchodilator and antispasmodic agent

Asthma is a chronic disease of respiratory system characterised by airway hyper responsiveness and lung inflammation leading to airway obstruction [1]. Bronchospasm can present as a significant life threatening perioperative complication in asthmatic patients [2]. Pathophysiological hallmark of the disease is eosinophil and lymphocyte infiltration. Conventional treatment options in asthmatic patients involve combination of bronchodilators and glucocorticoids. But both these drugs carry plurality of side effects. Treatment with bronchodilator alone will give the patient a relieving sensation while masking the progressive deterioration in the inflammatory process. It was known since long that treatment with lidocaine intravenously or as aerosol will prevent airway hyperactivity [3]. But in occasional patients aerosolized lidocaine itself can precipitate airway irritation, broncho-constriction and even a claustrophobic sensation [4]. When Groben et al compared the airway effects of lidocaine, dyclonine (more powerful local anaesthetic potency) and ropivacaine, they noted that lidocaine had a more powerful effect on attenuating bronchospasm [5]. This reflects that it is not the local anaesthetic potency of the molecule which is facilitating relief from bronchospasm. At this juncture it is relevant to recollect an interesting finding made by Ohnishi T et al wherein it was stated that the broncho-alveolar lavage of patients with bronchial asthma had

significant suppression of eosinophil viability [6]. The underlying mechanism is explained due to apoptosis and not due to cytotoxicity [7]. All these finding paving the way for a potential therapeutic use of lidocaine in bronchospasm therapy. Different formulations of lidocaine analogues were tried which has less of local anaesthetic property but have profound action on airway hyperactivity. JMF2-1 is a fluorinated lidocaine molecule with reduced anaesthetic action was one which was extensively evaluated initially [8]. But concerns were raised with JMF2-1 as it being a fluorinated analogue. Fluorinated compounds are known to cause potential adverse effects such as haemolytic anaemia and DNA damage [9]. So another analogue of lidocaine, JM25-1 was pharmacologically evaluated. This molecule was found to have limited impact on Na^+channels but more effective than the parent compound as a bronchodilator and anti-inflammatory agent [8]. This holds promise as a future bronchodilator and antispasmodic with fewer side effects of beta agonists and steroids.

Antiarrythmic agent

Lidocaine has a well established role as an antiarrhythmic agent. It is recommended as per advanced cardiac life support guidelines (ACLS) for the treatment of acute haemodynamically compromising ventricular arrhythmias. This can happen following myocardial ischemia / infarction or during cardiac manipulations (during cardiac surgery, cardiac catheterization) [10]. At the molecular level, lidocaine acts as a membrane stabilizing agent. It acts on the sodium channel in the inactive state and inhibits its recovery after repolarisation. Thus ventricular arrhythmias are controlled by suppressing the automaticity and spontaneous depolarization of the ventricular diastole.

Antitumor Action?

There is evidence to show that lidocaine and other local anaesthetic drugs can potentiate chemotherapeutic agents in vivo. Murakami et al has shown that when photofrin was dissolved in lidocaine jelly during photodynamic therapy, the effect was greater than direct application of photofrin alone [11]. Lidocaine and Dibucaine are known to enhance the cytotoxic effect of the antitumor antibiotic bleomycin [12]. Recently Lirk et al has shown that at clinically relevant doses, Lidocaine exerts demethylating effects on breast cancer cells [13]. Ropivacine was also shown to have the same effects on specific cancer cell lines [13]. A decrease in methylation can reactivate tumour suppressor genes and will help to arrest tumour growth. Another interesting finding of this in vitro study was the additive effect of lidocaine in combination with chemotherapeutic agent 5-aza-2'-deoxycytidine [13].

Antibacterial and Antiviral?

Numerous studies have shown the bacteriostatic, bactericidal, fungistatic and fungicidal properties of local anaesthetics against wide spectrum of microorganisms [14]. Interestingly, local anaesthetics differ in their antimicrobial potency also. Bupivacaine and Lidocaine has significantly more action on the microbes compared to ropivacaine [14]. Zekine Begec et al has shown that Lidocaine significantly inhibited the growth of S. aureus, E. coli and P. aeruginosa [15]. When mixed with Propofol, Lidocaine 2% was found to reduce not only the pain of injection but also found to reduce the harmful consequences of possible microorganism contamination [16]. Preservatives in Lidocaine were found to have no bacteriocidal activity, but weak bacteriostatic action only [17]. The perceived mechanism of local anaesthetics against antimicrobials is believed to be by disruption of microbial cell membrane permeability, leading to leakage of cellular components and cell destruction [14]. More research needed to confirm whether local anaesthetics can act as an adjunct to traditional antimicrobials. But in view of its proven antimicrobial actions, caution is to be exercised while administering local anaesthetics prior to any diagnostic procedures.

Conclusion

Lidocaine's pharmacological indications as local anaesthetic and antiarrythmic agent are well

recognized. But there is ample evidence in current literature to support the use of this molecule as an antitumor agent, antimicrobial, and as a bronchodilator. There is scope for further extensive pharmacological research before Lidocaine is used regularly for these extended indications.

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